

**ECONOMIC DECISION ANALYSIS FOR
HEALTHCARE SERVICE: THEORY AND PRACTICE**

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The Academic Faculty

by

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ECONOMIC DECISION ANALYSIS FOR HEALTHCARE SERVICE: THEORY AND PRACTICE

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SUMMARY

Health care service system is complex both in its complicated delivery design and in scientific and regulatory requirement. It is high cost, high risk, dynamic, and unpredictable. On one hand, healthcare service providers are challenged by high R&D cost, inefficient process management, variability in quality and necessity of changes to avoid the unanticipated consequences of new regulations. On the user end, they are overwhelmed by the complex service pricing and government regulations, as they often make decisions with asymmetric information with little understanding of what's best and available in the market. To help guide providers and users and to advance healthcare service research, we carry out theory and practice studies to better understand current issues and provide reasonable decision making framework.

In this dissertation, we investigate three broad topics: 1) Network effect on provider and customer dynamics. We perform theoretical analysis of health insurance competitions, and experimental design of proverse selection and network externality in a generalized transaction market. 2) Practice variance and systems analysis for quality and process improvement and new clinical guidelines establishment. This includes a system-approach study of post-operative care in pediatric congenital heart surgery, and investigation of a needle-based epidural procedure in obstetric anesthesia. 3) Computational in-silico drug design and its impact to service delivery for day-to-day healthcare needs and response to emerging diseases.

We first develop theoretical framework for a two-sided market framework to model competition between a Preferred Provider Organization (PPO) and a Health Maintenance Organization (HMO). Both health plans compete to attract policyholders and providers. Our game-theoretical framework examines the consequences of this risk segmentation on

providers and the network effect on policyholders based on market information and network size. The outcome of competition mainly depends on two effects: a market share effect and an adverse selection effect, captured by policyholders' surplus expectations on both policies and copayments. If the adverse selection effect is strong enough, the HMO plan takes advantage on competition. On the contrary, if the market share effect dominates, the PPO profit is higher in spite of the unfavorable risk segmentation and higher premium. Next, we expand our analysis to investigate proverse selection and network externality and its effect on consumers and providers in a generalized transaction market. Our framework establishes consumer's utility function and provider's profit function in terms of network indirect externality. We test the responses of both sides using an agent-based model; and establish the empirical design to enhance a "balanced" level of consumer's utility and provider's profit. We highlight a decision support framework for the consumers, the providers, along with the market regulators that enables an optimal social welfare.

In the second topic, we aim to analyze patient care process variation to establish new clinical guidelines for substantial process and quality improvement. In the post-operative care study of congenital heart surgery, we identify and summarize numerous practice variations within the post-operative care process. Specifically, we pinpoint various process/decision points along the post-op care continuum in which difference in care coordination, management, resources and practice may lead to significant impact and reasons for the difference in the length of stay among the five clinical sites. Using clustering and machine learning approaches, we rank the significance of these factors in predicting and influencing the length of stay of the patients. We compare current process to improved one using simulation model to demonstrate evidence in LOS improvement. Next, we generalize the study to establish and quantify the safety and efficacy of large dose needle-based epidural technique in obstetric anesthesia. The time and dose required to achieve the desired sensory level is quantified. We establish a safe and quickly effective epidural dose

that can be administered through the epidural needle prior to the insertion of the epidural catheter. Based upon these clinical findings, safe dosage parameters for injections as large as 20 milliliters through the epidural needle are quantified. Physician preference for medication and dosing levels are contrasted. Understanding the causes and effects of such variations can help providers and healthcare organizations in avoiding practices that negatively impact outcomes. These findings facilitate the establishment of new epidural practice guidelines and delivery improvement.

In the third topic, we describe the first in-silico drug design system model to accelerate drug discovery. Our model spans preclinical research, the IND review, clinical research, and the NDA review. We identify the global process for any drug discovery pathway with timeline along the entire system process. Next, we identify bottlenecks, and perform system optimization that offers a holistic view of discovery pathways. The integration of bottlenecks into possible candidate tasks which can be conducted simultaneously highlights critical paths for the accelerated development process. We define the critical paths as parallel model for the new drug development. Our generalized parallel model allows not only rapid development but also processes that minimize risk, cost, and time.

CHAPTER I

OVERVIEW OF ECONOMIC DECISION ANALYSIS IN HEALTHCARE INDUSTRY

For many years, natures of healthcare industry have been considered extremely complicated. Recent years have seen numerous complexities, risks or uncertainties in healthcare industry. These complicated issues in healthcare industry cause various concerns in economic side which should be addressed by healthcare service providers as well as healthcare service users. Moreover, clinical practices separately performed by various players in healthcare industry do not guarantee the optimal achievements because more parameters, variables, and effects have to be taken into account to determine the best course of actions. As a result, both theoretical and practical approaches need to be maintained to support decision analysis in healthcare industry. The applicability of the ideas that both theory and practice are required in decision analysis framework can fill the gap between research and clinical practice, which has been considered a major issued in evidence-based healthcare. In major clinical areas, it has long been acknowledged that the findings of research studies into what is effective often do not translate into actual practice[1]. Thus, choosing research approach toward either theory or practice should be appropriately addressed to help guide providers and users and to advance healthcare service research. In the following sections, we briefly suggest some possible approaches in applying theoretical and practical research method.

Network effect on provider and customer dynamics. An important and challenging aspect in not only healthcare industry but also outside healthcare entails understanding

market structure and its dynamics. Identifying provider and user, setting payment scheme, transaction logic can be modeled as microeconomic analysis theory such as game theory and two-sided market. With the solutions derived from such theory, we can establish the decision analysis strategy to correspond to market dynamics, particularly characterized by a network externality when an increase in the number of users/providers increases the value to other side. However, these theoretical solutions sometimes do not reflect actual market trends. Therefore, with the solutions derived from theoretical study, experimental design under various conditions could explain the difference between theoretical solutions and actual market dynamics.

Practice variance and systems analysis for quality and process improvement.

Current healthcare environment is characterized by substantial practice variation – some of which have negative consequences in the delivery of recommended care[2-7]. Identifying practice variance and the associated processes and/or factors may offer opportunities for improving care delivery and clinical outcome. Specifically, understanding theoretical background of clinical practice along with identifying various process points over the patient care can provide potential of stimulating new ideas for investigation or new management techniques, and increases provider's ability to conduct a highly specialized clinical setting.

Computational in-silico drug design. The drug discovery and drug development is long, costly and complex process[8]. Implementing new strategy in drug development requires practical process innovation to accelerate drug development. Here, theoretical and practical approach involves three major pieces 1) identifying critical processes in each phase on drug development, 2) building critical process model to accelerate drug development, and 3) suggesting possible scenarios to reduce cycle time from beginning to marketing in drug development.

In this dissertation, we investigate three broad topics: 1) Network effect on provider and customer dynamics. We perform theoretical analysis of health insurance competitions, and experimental design of proverse selection and network externality in a generalized transaction market. 2) Practice variance and systems analysis for quality and process improvement and new clinical guidelines establishment. This includes a system-approach study of post-operative care in pediatric congenital heart surgery, and investigation of a needle-based epidural procedure in obstetric anesthesia. 3) Computational in-silico drug design and its impact to service delivery for day-to-day healthcare needs and response to emerging diseases.

In the first topic, we first develop theoretical framework for a two-sided market framework to model competition between a Preferred Provider Organization (PPO) and a Health Maintenance Organization (HMO). Both health plans compete to attract policyholders and providers. Our game-theoretical framework examines the consequences of this risk segmentation on providers and the network effect on policyholders based on market information and network size. The outcome of competition mainly depends on two effects: a market share effect and an adverse selection effect, captured by policyholders' surplus expectations on both policies and copayments. If the adverse selection effect is strong enough, the HMO plan takes advantage on competition. On the contrary, if the market share effect dominates, the PPO profit is higher in spite of the unfavorable risk segmentation and higher premium.

Next, we expand our analysis to investigate proverse selection and network externality and its effect on consumers and providers in a generalized transaction market. Our framework establishes consumer's utility function and provider's profit function in terms of network indirect externality. We test the responses of both sides using an agent-based model; and establish the empirical design to enhance a "balanced" level of

consumer's utility and provider's profit. We highlight a decision support framework for the consumers, the providers, along with the market regulators that enables an optimal social welfare.

In the second topic, we aim to analyze patient care process variation to establish new clinical guidelines for substantial process and quality improvement. In the post-operative care study of congenital heart surgery, we identify and summarize numerous practice variations within the post-operative care process. Specifically, we pinpoint various process/decision points along the post-op care continuum in which difference in care coordination, management, resources and practice may lead to significant impact and reasons for the difference in the length of stay among the five clinical sites. Using clustering and machine learning approaches, we rank the significance of these factors in predicting and influencing the length of stay of the patients. We compare current process to improved one using simulation model to demonstrate evidence in LOS improvement.

Next, we generalize the study to establish and quantify the safety and efficacy of large dose needle-based epidural technique in obstetric anesthesia. The time and dose required to achieve the desired sensory level is quantified. We establish a safe and quickly effective epidural dose that can be administered through the epidural needle prior to the insertion of the epidural catheter. Based upon these clinical findings, safe dosage parameters for injections as large as 20 milliliters through the epidural needle are quantified. Physician preference for medication and dosing levels are contrasted. Understanding the causes and effects of such variations can help providers and healthcare organizations in avoiding practices that negatively impact outcomes. These findings facilitate the establishment of new epidural practice guidelines and delivery improvement.

In the last topic, we describe the first in-silico drug design system model to accelerate drug discovery. Our model spans preclinical research, the IND review, clinical research, and the NDA review. We identify the global process for any drug discovery pathway with timeline along the entire system process. Next, we identify bottlenecks, and perform system optimization that offers a holistic view of discovery pathways. The integration of bottlenecks into possible candidate tasks which can be conducted simultaneously highlights critical paths for the accelerated development process. We define the critical paths as parallel model for the new drug development. Our generalized parallel model allows not only rapid development but also processes that minimize risk, cost, and time.

CHAPTER II

NETWORK EFFECT ON PROVIDER AND CUSTOMER DYNAMICS

An important and challenging aspect in not only healthcare industry but also outside healthcare entails understanding market structure and its dynamics. Identifying provider and user, setting payment scheme, transaction logic can be modeled as microeconomic analysis theory such as game theory and two-sided market. With the solutions derived from such theory, we can establish the decision analysis strategy to correspond to market dynamics, particularly characterized by a network externality when an increase in the number of users/providers increases the value to other side. However, these theoretical solutions sometimes do not reflect actual market trends. Therefore, with the solutions derived from theoretical study, experimental design under various conditions could explain the difference between theoretical solutions and actual market dynamics.

In this chapter, we perform theoretical analysis of health insurance competitions, and experimental design of proverse selection and network externality in a generalized transaction market.

2.1 Competition Strategy for Healthcare Insurance Plans

In this section, we first develop theoretical framework for a two-sided market framework to model competition between a Preferred Provider Organization (PPO) and a Health Maintenance Organization (HMO).

2.1.1 Introduction

The health insurance exchanges established by the Affordable Care Act(ACA) opened in October 2013, potentially auguring a new era for the insurance industry and American health care overall[9]. Approximately eight million US residents currently obtain private health insurance coverage through one of the marketplaces created by ACA[10]. When fully implemented, the ACA is expected to increase the number of Americans with insurance by more than thirty million[11]. One of the key aspects of the ACA is new era of the health insurance marketplace where consumers can shop for private plans with different cost sharing. Taking account this aspect, consumers would expect various choices and appropriate premiums from health insurance marketplace. However, consumers' selection pools have been restricted since ACA was initiated because insurers use restricted or "narrow" provider networks in marketplace plan[12]. Actually, insurance plans that only allow coverage for a limited set of providers are growing in popularity under ACA[13]. Insurers are likely to continue to use narrow networks as a strategy to keep premiums affordable. These limited networks, which can steer consumers to lower cost providers, have been proposed as a solution to rising health care costs[14]. One of the reasons why insurers prefer to keep the "narrow network" strategy is fear of adverse selection which might be happened in the health insurance exchange market. Adverse selection is often presented as a major problem for competitive health insurance markets[15]. This

phenomenon occurs when premiums set by health plans do not perfectly reflect the heterogeneity in policyholders' health risk. In health insurance markets, the complicating factor is risk segmentation. This imperfect risk adjustment can be caused by different reasons. For example, it may be impossible or too costly for insurers to set differentiated premiums taking into account the risk factors that would reflect this heterogeneity[16]. Also, the regulation of health insurance exchange settled by current ACA prevents health plans from setting discriminated premiums in an individual risk adjustment fashion. Moreover, when policyholders subscribe health insurance contracts linked to their jobs, employers often supply a menu of health insurance plans with pre-set employee premiums[17]. In this case, health plans' premiums reflect differences in average total cost and not in individual expected health expenditure.

Traditional economics would suggest that the entry of more insurance plans into the health plan exchange market would lead to premium competition among the plans as each tries to get the policyholders' contracts. Premiums would get bid down to marginal costs. However, the nature of health insurance competition is more complex than this traditional model. Cutler and Reber observed that policyholders might be tempted, in an attempt to look for health plans that supply coverage with the lowest possible premium, to withdraw from plans that attract higher risks than himself[18]. In a dynamical setting, this behavior can lead to a "death spiral" phenomenon whereby less restrictive plans attract high risks and therefore repel low and medium risks, with a cumulative effect[19]. It is commonly acknowledged that high risk policyholders choose generous plans whereas low risks seek lower prices[20]. Since premiums are set by the average cost of a health plan's policyholders, the expected surplus of a policyholder depends on the characteristics of the other enrollees. This nature of the expected surplus can explain why "death spiral" happens in generous plans such as PPO.

Another component of health insurance plan selection has to do with the structure of insurance products, which introduces both path dependence and nonlinearity into the decision problem through various contractual components such as deductibles, out-of-pocket maximums, coinsurance and copayment options, and different treatment of providers that are preferred or non-preferred under the insurance policy[21]. Also, the decision problem relates to the policyholder's personal preferences and behavior. For example, there is a tendency for higher risk consumers to select PPOs and lower risk policyholders to enroll in HMOs[18, 19, 22, 23]. Bardey and Rochet first attempted to model the two-sided nature of the health plans' competition characterized by indirect network externalities between providers and policyholders' sides[16]. They consider an asymmetric duopoly situation to model competition between a PPO and an HMO. However, they focus on the case where health plans do not compete for the same physicians, therefore the two health plans have access to distinct pools of physicians. Gollier analyzes optimal insurance contract when the policyholder faces uncertainty about the distribution of his potential health risk[24]. Another research on asymmetric information in insurance market under two-sided market structure has been conducted and it concludes that competition cannot work properly and actuarially fair insurance is almost impossible[25]. Taking premium and copayment into account together, two-part pricing contract has been investigated to cover different types of policyholders[26].

In this paper, we develop theoretical framework for a two-sided market framework to model competition between a Preferred Provider Organization (PPO) and a Health Maintenance Organization (HMO). Both health plans compete to attract policyholders and providers. Our game-theoretical framework examines the consequences of this risk segmentation on providers and the network effect on policyholders based on market information and network size. The outcome of competition mainly depends on two effects: a market share effect and an adverse selection effect, captured by policyholders' surplus

expectations on both policies and copayments. If the adverse selection effect is strong enough, the HMO plan takes advantage on competition. On the contrary, if the market share effect dominates, the PPO profit is higher in spite of the unfavorable risk segmentation and higher premium.

2.1.2 The Model Structure

Three kinds of players are considered in the model. On the demand side, policyholders can become sick with an exogenous probability θ , which is heterogeneous across policyholders. The probability θ is distributed on $(0, 1)$ with pdf f and cdf F . On the provider side, physicians may decide to be affiliated with a health plan or not, according to the remuneration (R) offered. If physicians are affiliated with PPO, they only accept policyholders who have PPO plan, that is in-network patients only. Meanwhile, physicians who choose to be with HMO can accept PPO out-of-network patients as well as HMO in-network patients. There are two health plans between policyholders and physicians, indexed by i , with $i = \{P, H\}$ represents $\{PPO, HMO\}$ accordingly. Two health plans compete in health insurance contracts to attract policyholders and purchase healthcare services from physicians.

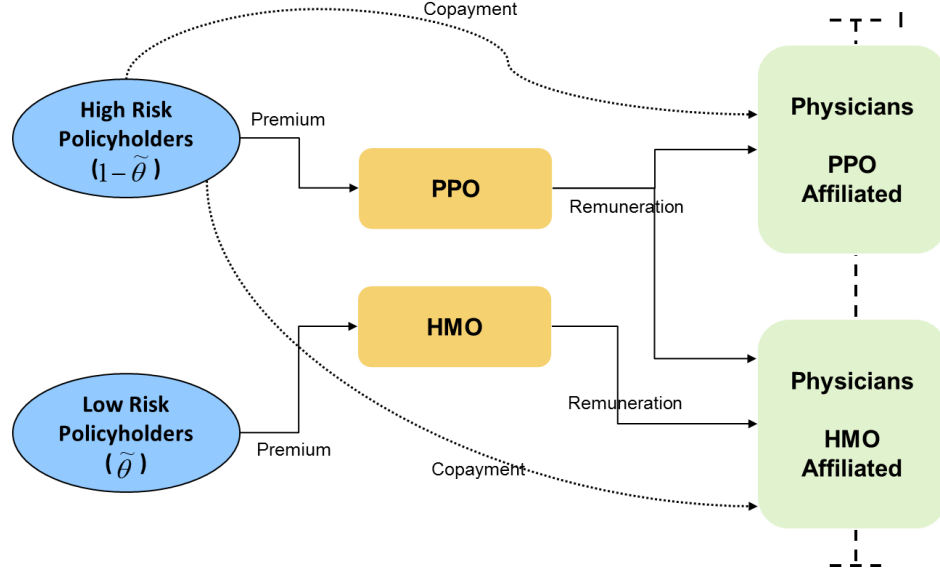


Figure 2- 1. Two-Sided Healthcare Insurance Market

Once potential policyholders approach health insurance market, PPO and HMO provide their premiums P_i and proportion of physicians (between 0 and 1) affiliated with network i which is denoted n_i . Thus, a higher n_i means more choices. If policyholders choose PPO, then copayment is incurred whenever they visit physicians. For the simplicity, we assume that there is no copayment in HMO plan. Actual HMO insurance plan generally charges small amount of copayment and no deductible on policyholders but they are negligible compare to PPO's copayment and deductible charge on policyholders.

Following Bardey and Rochet[16], we adopt their utility function for the policyholder. PPO policyholder's utility function is:

$$U_p = \theta(\lambda_p n_p + \lambda_H n_H - c_p - c_H) - P_p \quad 2.1.1$$

and HMO policyholder's utility function is:

$$U_H = \theta \lambda_H n_H - P_H \quad 2.1.2$$

where P_i is premium charged by each plan and n_i is proportion of physicians affiliated with plan i . c_p is copayment when PPO policyholder visits in-network physician and c_H

is copayment when he visits out-of-network physician. Finally, λ_p is policyholder's surplus derived from proportion of PPO network physicians which captures how policyholder values potential access to the affiliated physicians. Likewise, λ_H is policyholder's surplus derived from proportion of HMO network physicians.

We assume that health insurance plans are profit-maximization entities. The profit function of health insurance plan i is:

$$\Pi_i = D_i P_i - T_i \quad 2.1.3$$

where D_i is the number of policyholders affiliated with plan i and T_i the total transfer paid to physicians.

2.1.3 The Outcome of Competition Between Health Insurance Plans

We first analyze the determination of risk segmentation on policyholders' side. Then, we conduct physicians' side analysis. Finally, we find the global market equilibrium.

Risk Segmentation on the Policyholders' side

On the policyholders' side, the market shares between the PPO and the HMO, D_p and D_H respectively, decide the risk segmentation. Since we assume that higher risk policyholders tend to choose the PPO rather than the HMO, marginal indifferent level of policyholders between the PPO and the HMO is:

$$U_p(P_p, n_p) = U_H(P_H, n_H).$$

Therefore, the marginal policyholder's type $\tilde{\theta}$ is the one who is just indifferent between the PPO and the HMO:

$$\tilde{\theta} = \frac{P_P - P_H}{\lambda_P n_P + (\lambda_P - \lambda_H) n_H - (c_P - c_H)}. \quad 2.1.4$$

Physicians' Affiliation to Insurance Plans

Basically, we assume that each health plan has access to distinct groups of physicians. However, since the PPO policyholders can access out-of-network, physicians who are affiliated with the HMO can generate profit from both groups of policyholders. We adopt Bardey and Rochet model to understand physicians' side logic, which the number n_i of physicians who affiliated to health plan i is only function of the net profit level Φ_i offered by each health plan[16]. We assume that physicians uniformly located on a (0, 1) interval like Hotelling model and incur a transaction cost proportional to their distance with the PPO or the HMO. As a result, the number n_i of physicians is linear function: $n_i = \frac{\Phi_i}{\delta}$, where δ captures the transaction cost of the physicians and the sensitivity of the physicians' willingness to accept payment schemes offered by each health plan. If physicians are affiliated with plan i , they generate profit from a fee-for-service rate R_i offered by plan i and copayment c_i paid by the PPO policyholders.

Therefore, physicians' net profit levels when affiliated to the PPO and HMO are:

$$\Phi_P = \frac{\int_{\tilde{\theta}}^1 \theta dF(\theta)(c_P + R_P)}{n_P} \quad 2.1.5$$

and

$$\Phi_H = \frac{R_H \int_0^{\tilde{\theta}} \theta dF(\theta) + (R_P + c_H) \int_{\tilde{\theta}}^1 \theta dF(\theta)}{n_H}. \quad 2.1.6$$

Particularly, formula 2.1.5 shows the possibility of indirect network externality in the PPO plan. In other word, physicians who are affiliated with the PPO expect higher profit from the number of the PPO policyholders if the upper tail of the risk distribution is thick enough.

Thus, health plans should coordinate the level of P_i and c_i on the policyholders' side and the level of R_i and c_i on the physicians' side. We assume that each health plan has distinct groups of physicians, thus:

$$\delta n_p^2 = (c_p + R_p) \int_{\tilde{\theta}}^1 \theta dF(\theta) \quad 2.1.7$$

and

$$\delta n_H^2 = R_H \int_0^{\tilde{\theta}} \theta dF(\theta) + (c_H + R_p) \int_{\tilde{\theta}}^1 \theta dF(\theta). \quad 2.1.8$$

The Health Insurance Plans' Profits and Maximization Problem

Using 2.1.7 and 2.1.8, the health insurance plans' profits are:

$$\Pi_p = D_p P_p - T_p = [1 - F(\tilde{\theta})] P_p - R_p \int_{\tilde{\theta}}^1 \theta dF(\theta) = [1 - F(\tilde{\theta})] P_p + c_p \int_{\tilde{\theta}}^1 \theta dF(\theta) - \delta n_p^2,$$

and

$$\Pi_H = D_H P_H - T_H = F(\theta) P_H - R_H \int_0^{\tilde{\theta}} \theta dF(\theta) = F(\theta) P_H + \delta n_p^2 - \delta n_H^2 + (c_H - c_p) \int_{\tilde{\theta}}^1 \theta dF(\theta).$$

Each plan selects (P_i, n_i) to maximize its profit. The first-order conditions with respect to P_p and P_H are:

$$\frac{\partial \Pi_p}{\partial P_p} = [1 - F(\tilde{\theta})] - f(\tilde{\theta}) P_p \frac{\partial \tilde{\theta}}{\partial P_p} - c_p \tilde{\theta} \frac{\partial \tilde{\theta}}{\partial P_p} = 0,$$

and

$$\frac{\partial \Pi_H}{\partial P_H} = F(\tilde{\theta}) + P_H f(\tilde{\theta}) \frac{\partial \tilde{\theta}}{\partial P_H} - (c_H - c_p) \tilde{\theta} f(\tilde{\theta}) \frac{\partial \tilde{\theta}}{\partial P_H} = 0.$$

Because

$$\frac{\partial \tilde{\theta}}{\partial P_p} = -\frac{\partial \tilde{\theta}}{\partial P_H} = \frac{1}{\lambda_p n_p + (\lambda_p - \lambda_H) n_H - (c_p + c_H)},$$

we obtain:

$$P_p = \frac{1 - F(\tilde{\theta})}{f(\tilde{\theta})} [\lambda_p n_p + (\lambda_p - \lambda_H) n_H - (c_p + c_H)] - \tilde{\theta} c_p, \quad 2.1.9$$

and

$$P_H = \frac{F(\tilde{\theta})}{f(\tilde{\theta})} [\lambda_p n_p + (\lambda_p - \lambda_H) n_H - (c_p + c_H)] - \tilde{\theta} (c_p - c_H). \quad 2.1.10$$

Using equation 2.1.4, we obtain:

$$\tilde{\theta} = \frac{P_p - P_H}{\lambda_p n_p + (\lambda_p - \lambda_H) n_H - (c_p + c_H)} = \frac{1 - 2F(\tilde{\theta})}{f(\tilde{\theta})} \cdot \frac{\lambda_p n_p + (\lambda_p - \lambda_H) n_H - (c_p + c_H)}{\lambda_p n_p + (\lambda_p - \lambda_H) n_H - c_p}. \quad 2.1.11$$

The first-order conditions with respect to n_p and n_H are:

$$\frac{\partial \Pi_p}{\partial n_p} = -P_p f(\tilde{\theta}) \frac{\partial \tilde{\theta}}{\partial n_p} - c_p \tilde{\theta} f(\tilde{\theta}) \frac{\partial \tilde{\theta}}{\partial n_p} - 2\delta n_p = 0,$$

and

$$\frac{\partial \Pi_H}{\partial n_H} = P_H f(\tilde{\theta}) \frac{\partial \tilde{\theta}}{\partial n_H} - 2\delta n_H - (c_H - c_p) \tilde{\theta} f(\tilde{\theta}) \frac{\partial \tilde{\theta}}{\partial n_H} = 0.$$

Using equation 2.1.9, 2.1.10, and 2.1.11 with

$$\frac{\partial \tilde{\theta}}{\partial n_p} = \frac{\lambda_p}{\lambda_p n_p + (\lambda_p - \lambda_H) n_H - (c_p + c_H)} \tilde{\theta} \quad \text{and} \quad \frac{\partial \tilde{\theta}}{\partial n_H} = -\frac{\lambda_p - \lambda_H}{\lambda_p n_p + (\lambda_p - \lambda_H) n_H - (c_p + c_H)} \tilde{\theta},$$

we obtain:

$$n_p = \frac{\lambda_p}{2\delta} \tilde{\theta} [1 - F(\tilde{\theta})], \quad 2.1.12$$

and

$$n_H = \frac{\lambda_H - \lambda_P}{2\delta} \tilde{\theta} F(\tilde{\theta}). \quad 2.1.13$$

Using equations 2.1.7 and 2.1.8, we find the fee-for service rates as:

$$R_P = \frac{\lambda_P^2}{4\delta} \tilde{\theta}^2 [1 - F(\tilde{\theta})] - c_P, \quad 2.1.14$$

and

$$R_H = \frac{(\lambda_H - \lambda_P)^2}{4\delta} \tilde{\theta}^2 F(\tilde{\theta}) - \frac{\lambda_P^2}{4\delta} \tilde{\theta}^2 \frac{[1 - F(\tilde{\theta})]^2}{F(\tilde{\theta})} - (c_H - c_P) \frac{1 - F(\tilde{\theta})}{F(\tilde{\theta})}. \quad 2.1.15$$

Finally, using equations 2.1.12 to 2.1.15, we obtain the premiums from 2.1.9 and 2.1.10:

$$P_P = \frac{1 - F(\tilde{\theta})}{f(\tilde{\theta})} \left\{ \frac{\lambda_P^2}{2\delta} \tilde{\theta} [1 - F(\tilde{\theta})] - \frac{(\lambda_P - \lambda_H)^2}{2\delta} \tilde{\theta} F(\tilde{\theta}) - (c_P + c_H) \right\} - \tilde{\theta} c_P, \quad 2.1.16$$

and

$$P_H = \frac{F(\tilde{\theta})}{f(\tilde{\theta})} \left\{ \frac{\lambda_P^2}{2\delta} \tilde{\theta} [1 - F(\tilde{\theta})] - \frac{(\lambda_P - \lambda_H)^2}{2\delta} \tilde{\theta} F(\tilde{\theta}) - (c_P + c_H) \right\} - \tilde{\theta} (c_P - c_H). \quad 2.1.17$$

By replacing premiums and physicians' numbers by their outcomes in the health insurance plans' profits, we obtain the profits:

$$\begin{aligned} \Pi_P = & \frac{\lambda_P^2}{2\delta} \tilde{\theta} [1 - F(\tilde{\theta})]^2 \left[\frac{1 - F(\tilde{\theta})}{f(\tilde{\theta})} - \frac{\tilde{\theta}}{2} \right] - \frac{(\lambda_H - \lambda_P)^2}{2\delta} \tilde{\theta} [1 - F(\tilde{\theta})]^2 \frac{F(\tilde{\theta})}{f(\tilde{\theta})} \\ & - [1 - F(\tilde{\theta})] \cdot \left[\frac{1 - F(\tilde{\theta})}{f(\tilde{\theta})} (c_P + c_H) - (1 - \tilde{\theta}) c_P \right], \end{aligned} \quad 2.1.18$$

and

$$\begin{aligned}\Pi_H = & \frac{\lambda_P^2}{2\delta} \tilde{\theta} \left[1 - F(\tilde{\theta}) \right] \left[\frac{[F(\tilde{\theta})]^2}{f(\tilde{\theta})} - \frac{\tilde{\theta}}{2} \right] - \frac{(\lambda_H - \lambda_P)^2}{2\delta} \tilde{\theta} [F(\tilde{\theta})]^2 \cdot \left[\frac{F(\tilde{\theta})}{f(\tilde{\theta})} + \frac{\tilde{\theta}}{2} \right] \\ & + (c_H - c_P) \left\{ 1 - (1 - \tilde{\theta}) F(\tilde{\theta}) \right\} - \frac{F(\tilde{\theta})}{f(\tilde{\theta})} (c_P + c_H)\end{aligned}\quad 2.1.19$$

2.1.4 Analysis of the Outcomes

In this section, we analyze the meaning of the outcomes in the above section. First of all, the market segmentation determined by policyholders' risk level is found as equation 2.1.

11. We assume that $\lambda_i n_i$ is large enough so that $\lambda_i n_i - c_i$ is always positive. Since the marginal policyholder's type $\tilde{\theta}$ lies on (0, 1), equation 2.1.11 is:

$$\tilde{\theta} = \frac{P_P - P_H}{\lambda_P n_P + (\lambda_P - \lambda_H) n_H - (c_P + c_H)} = \frac{1 - 2F(\tilde{\theta})}{f(\tilde{\theta})} \cdot \frac{\lambda_P n_P + (\lambda_P - \lambda_H) n_H - (c_P + c_H)}{\lambda_P n_P + (\lambda_P - \lambda_H) n_H - c_P} > 0,$$

and it means $F(\tilde{\theta}) < \frac{1}{2}$. Therefore, the demand of the PPO, D_P , is always more than a half

of the market. In other word, the market share of the PPO is always higher than the HMO under two-sided market competition. Recent industry report supports our finding that fifty-two percent of covered workers are enrolled in PPOs in 2015. The PPO's market share in health plans has maintained over fifty percent of covered workers since 2002.

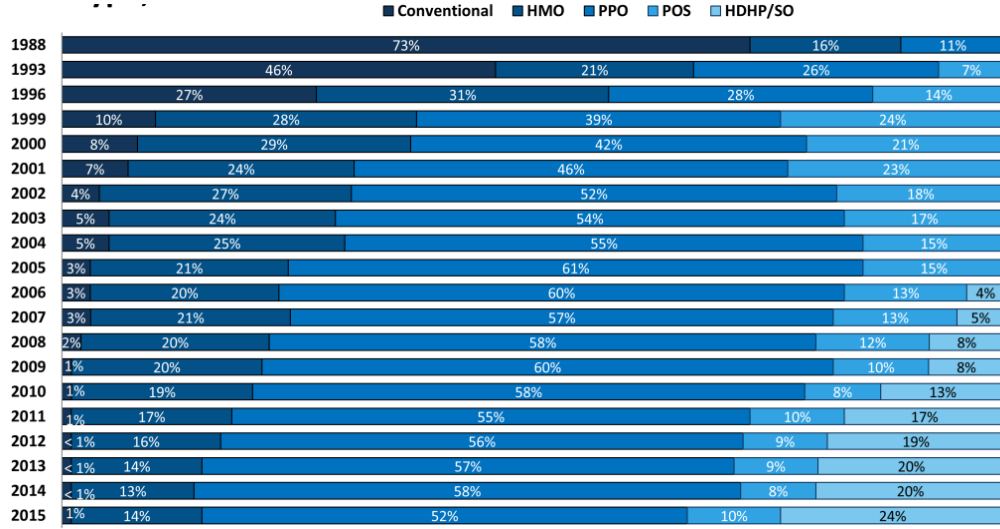


Figure 2- 2. Distribution of Health Plan Enrollment for Covered Workers, by Plan Type, 1988-2015. Source: Kaiser, KPMG and HIAA

Secondly, we investigate the implications of physicians' affiliation with each plan. From equations 2.1.12 and 2.1.13:

$$n_P - n_H = \frac{\tilde{\theta}}{2\delta} (\lambda_P - \lambda_H F(\tilde{\theta})). \quad 2.1.20$$

We assume that the expected surplus of the HMO policyholder, λ_H is larger than the others, λ_P . When people choose the HMO rather than the PPO, they tend to believe that less flexible services offered by the HMO are substantially workable for their health risks[18]. With equations 2.1.12, 2.1.13 and 2.1.20, the affiliated numbers of physicians for each plan depends on both indirect network externalities described by market segmentation and direct network externalities described by policyholders' valuations on physicians' side. More specifically on policyholders' valuations, if the expected surplus of the HMO network access is slightly larger than the expected surplus of the PPO network access, that is $\lambda_P < \lambda_H < \frac{\lambda_P}{F(\tilde{\theta})}$, then the size of the PPO physicians' network (n_P) is bigger than the size of the HMO physicians' network (n_H). If the expected surplus of the HMO network access

is much larger than the expected surplus of the PPO network access, that is $\lambda_H > \frac{\lambda_p}{F(\tilde{\theta})}$, then the size of the HMO physicians' network (n_H) is bigger than the size of the PPO physicians' network (n_p). Therefore, we can find that the physicians' side prefers to join the PPO when the market share effect dominates on the policyholders' side while the physicians' side prefers to join the HMO when the adverse selection effect dominates on the policyholders' side.

Thirdly, we analyze the conditions how each health insurance plan offers remunerations to the affiliated physicians' group. We assume that in-network copayment c_p is less than out-of-network copayment c_H . From equations 2.1.14 and 2.1.15, R_p is bigger than R_H when $\lambda_p < \lambda_H < \frac{\lambda_p}{F(\tilde{\theta})}$ and the opposite holds when $\lambda_H > \frac{\lambda_p}{F(\tilde{\theta})}$. Thus, similar standard also can be held in remuneration scheme likewise physicians' network. If the market share effect dominates, the PPO offers higher fee-for-service level, R_p , to maintain bigger size of affiliated physicians' group while if the adverse selection effect dominates, then the HMO offers higher fee-for-service level, R_H .

Finally, each health insurance plan's profit is determined as equation 2.1.18 and 2.1.19. Then,

$$\Pi_P - \Pi_H = \left\{ \lambda_p^2 [1 - F(\tilde{\theta})] - (\lambda_H - \lambda_p)^2 F(\tilde{\theta}) \right\} \cdot \frac{\tilde{\theta}}{2\delta} \left[\frac{1 - 2F(\tilde{\theta})}{f(\tilde{\theta})} + \frac{\tilde{\theta}}{2} F(\tilde{\theta}) \right] - (c_H - c_p) \Gamma(\tilde{\theta})$$

where $\Gamma(\tilde{\theta})$ is function of probability distribution, $0 \leq \Gamma(\tilde{\theta}) \leq 1$. In this analysis, the similar conditions from above also can be held. If the market share effect dominates, i.e.

$\lambda_p < \lambda_H < \frac{\lambda_p}{F(\tilde{\theta})}$, the profit of the PPO is higher while if the adverse selection effect

dominates, that is $\lambda_H > \frac{\lambda_p}{F(\tilde{\theta})}$, the profit of the HMO is higher. It is worth to denote the role of the copayments even though the copayments are significantly less than premiums. Recall that in-network copayment c_p is less than out-of-network copayment c_H . The last term $(c_H - c_p)\Gamma(\tilde{\theta})$ is only related on the PPO plan. If the PPO sets out-of-network copayment, c_H , to be too high, then the PPO makes losses on own profit. Although the lower level of out-of-network copayment might not directly harm the profit of the PPO directly, we might conject that the HMO could have flexibility in the market because the HMO can offer more attractive remuneration to the physicians' side and premium to the policyholders' side. Therefore, it is required for the PPO to maintain appropriate ratio between in-network copayment and out-of-network copayment not to lose its own potential profits.

2.1.5 Conclusion

In this paper, we analyze the outcome of competition between a PPO and an HMO. Our framework helps identify conditions how each plan can benefit competitive advantage corresponding two-sided market competition. We identify the two conditions: the market share effect described by segmentation of the policyholders supports the PPO's higher profit whereas the adverse selection effect described by the policyholders' higher expectation on the HMO plan leads the HMO's competitive advantage.

As mentioned in Bardey and Rochet[16], the two-sided market approach in healthcare insurance industry provides some important implications for public policy issues. The two-sided nature of health insurance market can explain the preference of higher flexibility that has been observed during the last 15 years in the US health insurance

market. However, current ACA prevents the insurance company from setting discriminated premiums in an individual risk adjustment fashion. We believe that the restriction of offering flexibility is the one of reasons why recent drop off rate increases in the health insurance exchange settled by ACA. The regulation needs to address two-sided logic in health insurance market rather than using one-sided logic. In such a context, policyholders can choose the plans according to their preferences and insurance plans may expand “wide network” strategy to benefit from competitive advantage.

Acknowledgment

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2.2 Experimental Design of Proverse Selection and Network Externality

In this section, we expand our analysis to investigate proverse selection and network externality and its effect on consumers and providers in a generalized transaction market.

2.2.1 Background

Two-sided market models provide a new perspective to view the platform-based industry such as credit cards, newspapers, telecommunications, internet services, computer operation systems and many more. Recent technology advances drive more industries to adopt two-sided market transactions. One of the reasons to adopt two-sided market transactions is network externality. Product and services that bring together groups of users in two-sided networks are platform[27]. They provide infrastructure and rules that facilitate the two groups' transactions and can take many guises. In some cases, platforms rely on physical products. In other cases, they are places providing services, like web sites or mobile connections. A key characteristic, here, is the presence of network externalities between these two groups. In markets with two-sided network externalities, the value that a group derives from joining a platform is determined by the number of the other group[28].

Most theories of network externalities are originated from the insight that characterizing network markets may require not only product standardization, essential to demand economies of scale[29, 30], it may also require recognizing sharp distinctions between consumer types[31]. With the network externalities addressed on historically, recent two-sided market literature has shown various implications such as pricing[32-38], competition strategy[39-43], and market structure[27, 28, 37, 44-46]. In addition to two-

sided market literature, network externalities based on new technology adoption have been investigated[47-49].

However, markets with network externalities sometimes experience negative results because of the adverse selection behavior chosen by any distinct group in the market. Since Akerlof first formalized the theory of adverse selection[50], numerous researches have been aware of the potential for adverse selection in markets with information asymmetries[51]. In particular, healthcare insurance markets[16, 52-54], healthcare service markets[55], auctions[51], and financial asset markets[56, 57] have been emphasized that they might experience market failures that adverse selection can cause. Therefore, methods to detect adverse selection and avoid it are truly required for the policy makers as well as the groups in the market.

Another issue on network externalities is how they affect the diffusion and the consequent economic value associated with transaction. Despite the sizeable academic literature on the dynamics of network markets, the answer to this issue is not obvious[58]. One side of literature suggests that network effects drive faster market growth due to increasing returns associated with such processes. The other argues that networks can also create the opposite effect of slowing growth. For example, most consumers see little utility in the transactions, as there are few others both in the consumer group and in the provider group, and so they may take a “wait-and-see” strategy until there are more players in the market. In addition, we may observe that some of users tend to abandon the network market even after the diffusion and growth has been boosted. Recently, we see that Facebook and Twitter are losing users even though the contents providers based on them are still increasing. It is pretty interesting that this phenomenon is against the literature about the network externalities.

Therefore, there are important question to arise, 1) how to internalize the effects of network externality in the market, 2) with potential negative side of network externality, how to avoid adverse selection in the networked market and 3) as a result, how to establish a market structure that provides “proverse selection” which is characterized by benefits of network externality among participants in the market. In this paper, we first describe the theoretical model as we applied it to market transaction taking into account two-sided market structure reflecting on the network externality. Then, we establish the empirical design, with agent-based model, to enhance a “balanced” level of consumer’s utility and provider’s profit. We highlight a decision support framework for the consumers, the providers, along with the market regulators that enables an optimal social welfare.

2.2.2 The Theoretical Model

Platform

We consider a monopoly platform of a two-sided market. A platform provides market place where consumers and providers are connected with. The platform collects a subscription price p from each consumer who is willing to purchase services or products through the platform. Also, the platform collects a subscription price s from each provider to allow the services or products to reach the consumer. We assume that the platform only offers linear fee contracts, thus it does not offer any quantity discounts or exclusive contracts such as lump-sum fees and incentives. Finally, we assume that the cost of providing the platform service is c per consumer.

Consumers

Consumers are interested in accessing the platform to reach services or products from providers. A consumer i ’s location x_i , indexes his utility for accessing the platform and

interacting with providers. Consumers pay a “transaction cost” t per unit of distance “traveled.” Consumers’ locations are uniformly distributed on the interval $(0, 1)$ with the platform located $x = 0$ based on a generalized Hotelling model. This modeling setup is a common way in the two-sided market model and is consistent with Armstrong[59].

Consumer i ’s utility is specified as:

$$u_i = v + bn_p - tx_i - p \quad 2.2.1$$

where $v > c$ is an intrinsic value that a consumer receives from accessing the platform irrespective of the amount of services/products, b is the marginal value that a consumer places on an additional provider on the platform and n_p is the number of providers connected with the platform.

Providers

Providers depend on transaction revenue per consumer, a , to generate revenue. We assume providers to be uniformly distributed on the unit interval and have a unit mass. We make the simplifying assumption that providers do not compete with each other. Each provider then earns an_c , where n_c is the number of consumers paying the platform for access to providers. Thus, a is the value for a provider of an additional consumer connected with the platform.

Providers are heterogeneous in terms of the fixed costs of coming up with a business idea and setting up their business. A provider indexed by j faces a fixed “transaction” cost of fy_j , where y_j is the index of the provider’s location on the unit interval $(0, 1)$. Each provider may have to pay the platform a subscription fee, s , to gain access to consumers. Hence, a provider j ’s profit is:

$$\pi_j = an_c - fy_j - s . \quad 2.2.2$$

Demand

In this two-sided market, the demand for service/product relies on the expected amount of service/product provided since more consumers will connect to the network if more expected content is available. Moreover, the provision of service/product depends on the expected number of consumers. When the expected number of consumers is n_c^e and the expected number of providers is n_p^e , the marginal consumer x_i who is indifferent between subscribing to the platform not subscribing is located at:

$$x_i = n_c = \frac{v + bn_p^e - p}{t} . \quad 2.2.3$$

The marginal provider y_j indifferent between being active and exiting the market is located at:

$$y_j = n_p = \frac{an_c^e - s}{f} . \quad 2.2.4$$

We focus equilibrium expectations where each side's expectations are met. That is, $n_c^e = n_c$ and $n_p^e = n_p$. The number of consumers and providers is then given by the simultaneous solution from 2.2.3 and 2.2.4, which is:

$$n_c(p, s) = \frac{f(v - p) - bs}{ft - ab} , \quad 2.2.5$$

and

$$n_p(p, s) = \frac{a(v - p) - ts}{ft - ab} . \quad 2.2.6$$

Positivity of the demands requires $ft > ab$, and v to be sufficiently large, that is

$$v > p + \frac{bs}{f} \text{ and } v > p + \frac{ts}{a}.$$

Monopoly Platform Optimum

We now describe the monopoly platform optimum. The platform maximizes its profit with subscription prices, p and s :

$$\text{Max } \Pi(p, s) = (p - c)n_c(p, s) + sn_p(p, s) \quad 2.2.7$$

where c is platform's service cost for consumer.

The optimal p for the platform given s can be solved by $\frac{\partial \Pi}{\partial p} = 0$, which is:

$$p(s) = \frac{f(v + c) - s(a + b)}{2f}, \quad 2.2.8$$

and the optimal s for the platform given p can be solved by $\frac{\partial \Pi}{\partial s} = 0$, which is:

$$s(p) = \frac{av + bc - p(a + b)}{2f}. \quad 2.2.9$$

Solving equation 2.2.8 and 2.2.9 simultaneously, we can find the subscription prices charged on consumer and provider that maximizes the platform's profits.

$$p = \frac{(2ft - ab)(v + c) - b^2c - a^2v}{4ft - (a + b)^2}, \quad 2.2.10$$

and

$$s = \frac{(a - b)f(v - c)}{4ft - (a + b)^2}. \quad 2.2.11$$

The number of consumers is:

$$n_c = \frac{2f(v-c)}{4ft - (a+b)^2}, \quad 2.2.12$$

and the number of providers is:

$$n_p = \frac{(a+b)(v-c)}{4ft - (a+b)^2}. \quad 2.2.13$$

As a result, the monopoly platform's profits with above equations are:

$$\Pi(p, s) = \frac{f(v-c)^2}{4ft - (a+b)^2}. \quad 2.2.14$$

2.2.3 The Experimental Model

In order to examine how network externality drives market transactions, we use an agent-based modeling technique that simulates aggregate consequences derived from interactions between groups in the market. Agent-based models (ABM) are used to map actual situations in a “would-be-world” while keeping realistic relationships accurate at the individual level[58]. They are increasingly used in the several fields to model actual processes such as diffusion, collective action, and group influence[60, 61] as well as economic activity in general[62-64]. They are also increasingly used in the marketing literature, particularly with respect to new product growth[65-70].

Kiesling et al. suggested four methodological strengths of the ABM: 1) the ability to explicitly model decision making entities individually, 2) the ability to account for the interactions between entities, 3) the ability to address what-if-type questions, and 4) the ability to capture emergent market dynamics[63]. Since our research on network externality contains decision making and market dynamics as well as interaction among

multiple entities, the ABM technique enables us to contribute to establish a decision support framework for the consumers, the providers, along with the market regulators that enables an optimal social welfare.

Simulation Procedure

First of all, we assign all parameter values for the simulation. We assume that each consumer acts reasonably based on utility function from equation 2.2.1. Likewise, each provider follows equation 2.2.2. Both consumer and provider join the platform to make transaction observing the numbers of the other side. All parameter values are shown in table 2.1.

Table 2- 1. Parameter values in ABM simulation

	Consumer	Provider	Platform
Parameters	Intrinsic value(v) :		Service cost(c) :
	• fixed value		• fixed value
	Marginal value(b) :	Marginal value(a) :	
	• Uniform	• Uniform	
	• Log-Normal	• Log-Normal	
	• Gamma	• Gamma	
	Transaction cost(t) :	Transaction cost(f) :	
	• fixed value	• fixed value	
	Consumer location(x_i):	Provider location(y_i):	
	• Uniform	• Uniform	
	Subscription price(p):	Subscription price(s):	
	• fixed value	• fixed value	

Once the all parameter values are assigned, we generate simulation procedure increasing numbers of each side, i.e. consumer group and provider group. Then simulation procedure calculates utility value of each consumer based on numbers of provider group. Likewise, the procedure calculates the profit of each provider based on numbers of consumer group. Whenever transactions happen between consumers and providers, platform's profits are generated in terms of the numbers of both sides. In addition, the ABM simulation procedure generate additional measures to support market regulator's reactions. We adopt total surplus(TS) as a social welfare's standpoint, which is:

$$Total\ Suplus(TS)$$

$$= Platform's\ Profits(\Pi) + Consumer's\ Surplus(CS) + Total\ Provider's\ Profits(\pi_p)$$

$$\text{where } CS = \int_0^{n_c(p,s)} (v + bn_p(p,s) - tx - p) dx, \text{ and } \pi_p = \int_0^{n_p(p,s)} (an_c(p,s) - fy - s) dx.$$

Finally, we arbitrary maintain ratio between consumer and provider as 10:1. As a result, our ABM simulation runs until there exist 500 consumers and 50 providers who connect each other through the platform.

2.2.4 Results

In this section, we describe our findings on each entity based on ABM simulation group and interpret the implications.

Consumer

Now, we turn to the simulation results on consumer side. We test three different scenarios based on assigned parameter values. Figure 2-3 shows our ABM simulation results in consumer utility. First, we observe the three different stages, which we call them stage 1,

2 and 3. At stage 1, each consumer utility from all three scenarios gradually increases, practically very little deviation exists. At stage 2, the tendency of all scenarios is increasing but the shape of each scenario is different. Consumer's utility increases sharply in scenario 1 and 2 while it increases gradually in scenario 3. Also, the deviation of the scenario 2 is larger than the scenario 1. At stage 3, consumer's utility derived from each scenario does not increase any more. Consumer's utility from scenario 1 and 2 decreases as the numbers of provider still increases, particularly scenario 2 shows sharp drop down at stage 3. Meanwhile, consumer's utility from scenario 3 stays consistent level even the numbers of provider still increases.

The results in Figure 2-3 provide three clues in network externality. First of all, gradual increase of the consumer utility in stage 1 shows that "chilling effect" exists in two-sided market transaction. Initial network externality may have a chilling effect on growth due to the "wait-and-see" position adopted by consumers in unmaturing market. We can interpret that the very low growth rate of consumer utility proves that two-sided market structure also experiences chilling effect in the early stage of transactions. Therefore, companies who start up their business under two-sided market structure should induce more providers to affiliate with them. Secondly, explosion of the consumer utility in stage 2 shows that there exists indirect network externality effect in two-sided market structure. Finally, the finding in stage 3 is very interesting. The numbers of provider reach maximum level does not guarantee the maximum level of consumer utility. When the numbers of provider are large enough, consumer may be suffered from asymmetric information, which generally happens in networked market. Previous literature points out possibility of adverse selection caused by asymmetric information, in particular, when provider group has more information than consumer group. The tendency in stage 3 could reflect the possibility of adverse selection adopted by consumer. That is, too many providers exist in the market does not guarantee the maximizing consumer utility level. Hence, platform or market

regulator needs to control the numbers of provider at appropriate level. We will show this reasoning in social welfare analysis again.

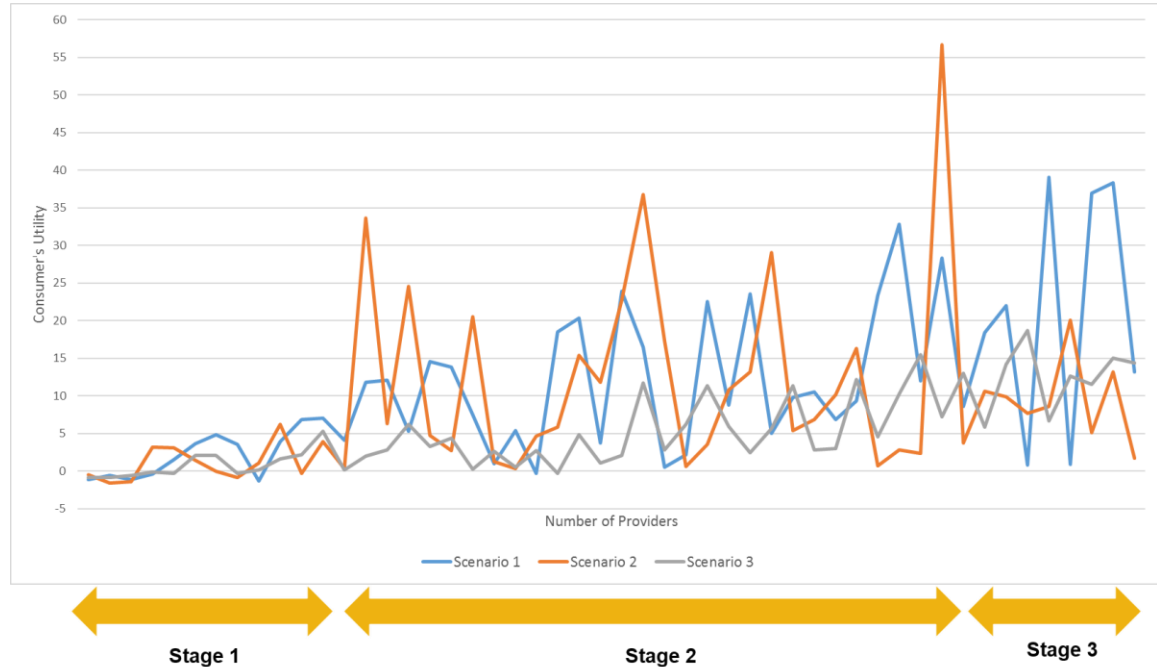


Figure 2- 3. Simulation results: consumer utility

Provider

Simulation results on provider side are rather straightforward. Figure 2-4 shows our ABM simulation results about provider profits. All three scenarios on provider profits increase steadily as the numbers of consumer increase. Provider can fully internalize the indirect network externality to generate its profits under two-sided market structure. Therefore, provider always expects the maximum profits when the numbers of consumer who affiliate with the platform are maximum.

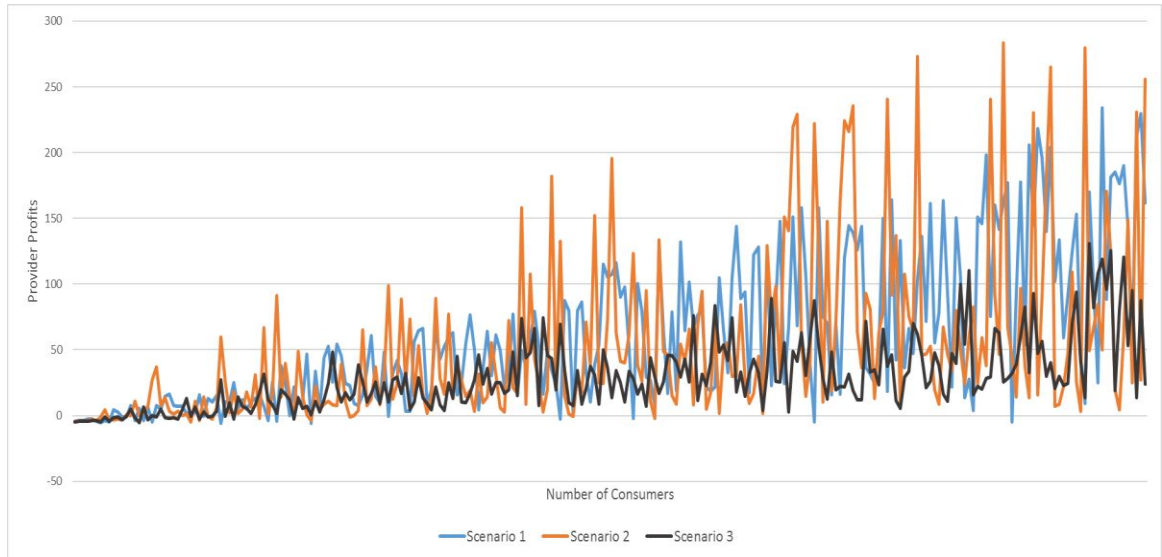


Figure 2- 4. Simulation results: provider profits

Platform

Next, we generate platform profits as the numbers of both sides change. Figure 2-5 shows the platform profits with the numbers of both sides. As we expect, platform profits have positive relationship with the numbers of consumer because platform can collect more subscription fee from providers as the numbers of consumer increase. However, platform profits do not increase any more when too many providers join the platform. Since consumer utility may drop down if there are too many providers in the market, some consumers choose not to affiliate with the platform rather than choose to make transactions through the platform. Then, the platform may experience profits to be falling down from the maximum profits level.

To prevent loss of profits, platform may choose two options. First one is preventing consumers from adverse selection. Platform may provide additional information balancing the status of asymmetric information on consumers' side. Informed consumers do not need to deviate from transactions through the platform, so the platform can maximize its profits.

Second option is controlling the numbers of provider. If the platform recognizes decreasing its profits, then the platform may reject additional providers who are willing to join.

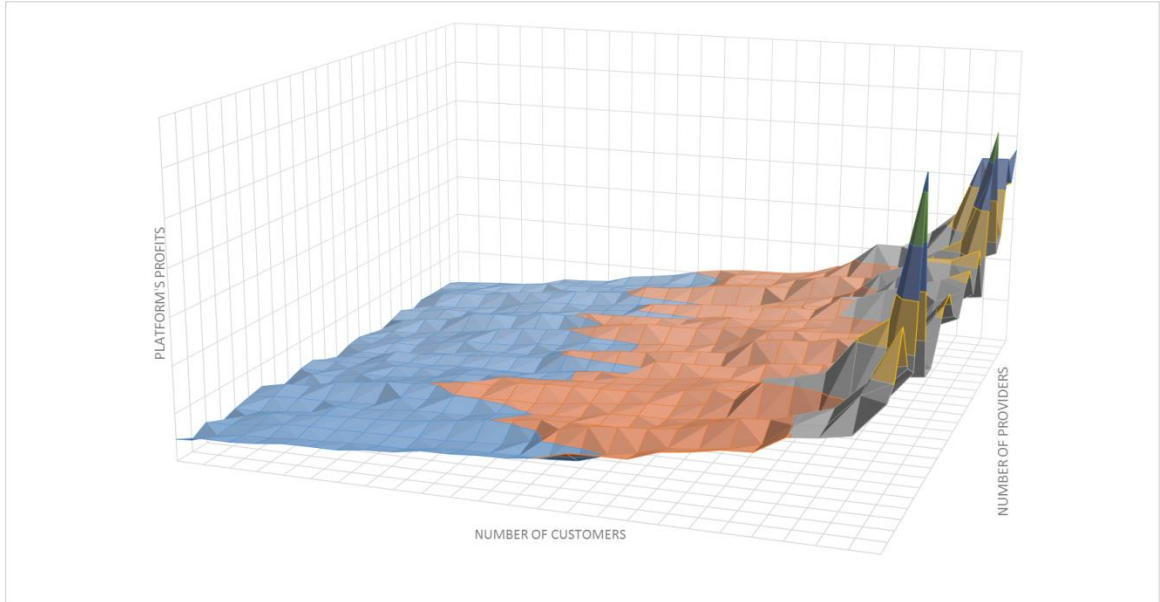


Figure 2- 5. Simulation result: platform profits

Social Welfare

Finally, we describe implications on regulator's standpoint. We use total surplus generated under two-sided market structure. Figure 2-6 shows the ABM simulation result in total surplus. Total surplus consists of three parts: platform profits, accumulated consumers' utility and total providers' profits. Therefore, total surplus in this market increases as the numbers of consumer increases because of platform profits and provider profits generated by the numbers of consumer. However, we can observe the decrease of total surplus even the numbers of provider still increase because they can affect consumer's utility and platform profits negatively. Hence, regulator needs to restrict the numbers of provider in the market. That is, too many providers in the market is not socially optimum. Proverse selection happens under appropriate numbers of provider.

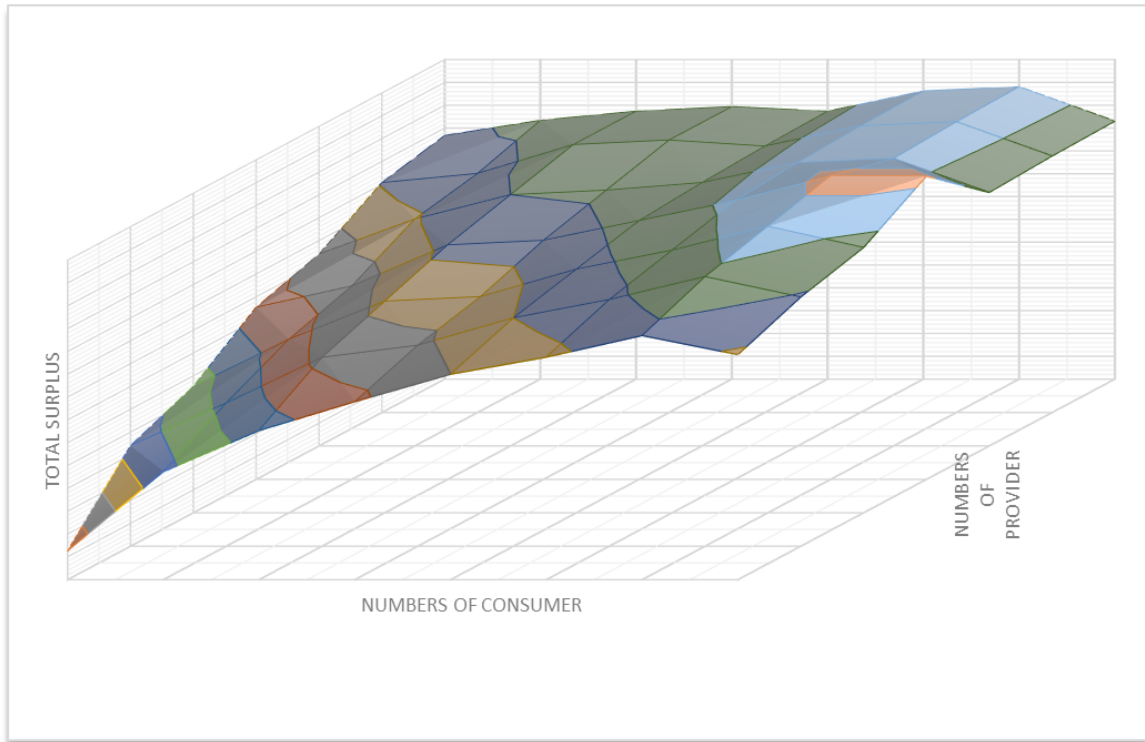


Figure 2- 6. Simulation result: total surplus

2.2.5 Conclusion

This paper focuses on understanding and analyzing proverse selection and network externality in two-sided networked market structure. We aim to identify effects from network externality and the associated behaviors that may offer opportunities for enjoying positive effects derived from network externality. First of all, we introduced monopoly two-sided market where general transactions occur between consumers group and providers group through the platform. Based on equilibriums under monopoly two-sided market structure, we ran agent-based model simulation to identify each entity's behavior taking account into network externality.

Our study reveals several intuitive results. First, a consumer can hesitate to make transactions with providers when the maturity of the two-sided market is early stage. Since consumer cannot be certain about the positive effect of network externality in terms of small numbers of provider, consumer can take wait-and-see strategy until enough numbers of provider access the platform. We can interpret that this chilling effect in the network externality causes troubles for startup companies who adopt two-sided market platform business. Secondly, both consumer and provider can fully internalize network externality once both sides have enough numbers in the market. Therefore, positive indirect network externality effect exists in the two-sided market structure. Thirdly, once the two-sided market is grown up, some consumers may deviate from the market transactions under adverse selection effect. Therefore, the platform needs to balance the information on both sides to maintain proverse selection strategy. Finally, regulator may choose to restrict entry of additional providers in the market to facilitate social optimum. Since we show the possibility of consumer's adverse selection, social optimum can be managed under appropriate numbers of provider.

Our experimental framework using agent-based model provides practical decision making model for both platform and regulator to manage proverse selection and social optimum. However, our model currently focuses on monopoly two-sided market structure. We expect two potential extensions from our model: 1) competitions between platforms and 2) social influence in network externality.

In conclusion, we see this paper as a starting point for studying the network externality under generalized two-sided market structure. We believe that our model highlights a decision support framework for the consumers, the providers, along with the market regulators that enables an optimal social welfare.

CHAPTER III

PRACTICE VARIANCE AND SYSTEMS ANALYSIS FOR QUALITY AND PROCESS IMPROVEMENT

Current healthcare environment is characterized by substantial practice variation – some of which have negative consequences in the delivery of recommended care[2-7]. Identifying practice variance and the associated processes and/or factors may offer opportunities for improving care delivery and clinical outcome. Specifically, understanding theoretical background of clinical practice along with identifying various process points over the patient care can provide potential of stimulating new ideas for investigation or new management techniques, and increases provider’s ability to conduct a highly specialized clinical setting.

In this chapter, we discuss two topics. Section 3.1 discusses practice variations within the post-operative care process. Specifically, we pinpoint various process/decision points along the post-op care continuum in which difference in care coordination, management, resources and practice may lead to significant impact and reasons for the difference in the length of stay among the five clinical sites[71]. In Section 3.2, we generalize the study to establish and quantify the safety and efficacy of large dose needle-based epidural technique in obstetric anesthesia. We establish a safe and quickly effective epidural dose that can be administered through the epidural needle prior to the insertion of the epidural catheter[72].

This chapter consists of content from two full papers, “Practice Variance Analysis for Process Improvement in Post-Operative Care of Congenital Heart Surgery, authored by

Eva K. Lee, Jinha Lee, Susan C Nicolson, Richard G Ohye, Lara S Shekerdemian, Madolin K Witte, Prashant D. Tailor, and William Mahle; and Investigating a Needle-Based Epidural Procedure in Obstetric Anesthesia, by Eva K Lee, Haozheng Tian, Jinha Lee, Xin Wei, John Neeld, Jr. K Doug Smith, and Alan R Kaplan.

3.1 Practice Variance Analysis for Process Improvement in Post-Operative Care of Congenital Heart Surgery

This section consists of the entire paper, “Practice Variance Analysis for Process Improvement in Post-Operative Care of Congenital Heart Surgery,” that is submitted to *Circulation*.

Practice Variance Analysis for Process Improvement in Post-Operative Care of Congenital Heart Surgery

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Abstract

This paper focuses on understanding and analyzing patient care process variation in post-operative care of congenital heart surgery. We aim to identify practice variance and the associated processes and/or factors that may offer opportunities for improving care delivery and clinical outcome. Focusing on five pediatric heart surgery sites, we have identified and summarized numerous practice variations within the post-operative care process.

Specifically, from a system viewpoint, we pinpoint various process points along the post-op care continuum in which difference in care coordination, management, resources and practice may lead to significant impact and reasons for the difference in LOS across the five sites.

Using clustering and machine learning approaches, we rank the significance of these factors in predicting and influencing the length of stay of the patients. In particular, ICU care, step-down care, and early extubation offer the highest potential of returns. The strength of this study is that by combining direct observations and data collecting, interviews, system process map design, system simulation, and machine learning together, we can identify and prioritize major practice variance and key factors that may influence clinical outcome. The findings can be readily presented in a systematic manner to the hospitals for potential process improvement. As a result of this study, a collaborative learning study has been started with a new clinical practice guideline (CPG) established for early extubation for a selected group of patients. A clinical trial involving these five sites, using the new CPG, began in April 2014, A clinical paper is currently in preparation to discuss the design of the collaborative study and the establishment of the CPG protocol.

3.1.1 Introduction

Numerous studies have shown that surgical outcomes differ among congenital heart centers. One possible reason for these differences is that the current healthcare environment is characterized by substantial practice variation – some of which have negative consequences in the delivery of recommended care[2-7]. Due to the innate variation in patient symptoms, patient diseases, provider training, provider experience, health system design, and resource allocation, variation cannot be completely removed in healthcare[73-

76]. However, understanding the causes and effects of variation can help providers and healthcare organizations avoid practices that negatively impact outcomes.

Practice variance is the difference in care between two similarly diagnosed patients that causes difference in length of stay (LOS) in the hospitals. Practice variance leads to variations in care quality, inefficient use of resources, fewer patients being treated, increased costs for both patient and hospitals, poor hospital utilization and increased patient susceptibility. Practice variance is an important issue to analyze as a means to optimize care outcome and delivery.

In previous studies, various attempts to identify the nature of practice variation have been made. Studies have found associations between physicians[77, 78], geographic locations, and institutions[2, 79]. Furthermore, research suggests how to optimize appropriate level of practice variation with resource utilization[77, 80] and decision making processes[78]. Additional research suggests implementing practice guidelines to multi-clinical institutes improves standardized care and reduces highly variable results[81-84]. Comparing resources, decision making and patient care between institutions might reveal the exact points of practice variance and help identify critical factors in reducing it, yet to date this has not been examined.

With this framework in mind, this paper aims to study patient care process variation, particularly from the provider standpoint in post-operative care of congenital heart surgery. In each hospital, physicians, nurses, and other hospital staff interact with each other and with patients in different ways. They also use resources differently. Specifically, we focus on four areas:

1. *Identify post-op care processes from each hospital and highlight practice variations on clinic and care management workflow.* Because this study involves multiple

hospitals, we first focus on identifying overall post-op care processes in intensive care unit (ICU), cardiac step-down unit (CSU), patient hand-off from operating room (OR) to ICU, and patient hand-off ICU to CSU in each hospital.

2. *Understand practice variation among multiple hospitals and its contribution to different outcomes based on different resources, decision making process and care management style.* Each hospital possesses different care resources; for example, a care team may consist of physicians, respiratory therapists, and registered nurses. The care team makes different care decisions based on its resource availability. The variation often results in different care plans for similar conditions.
3. *Identify key factors that affect LOS using a computerized system model.* Combining on-site observations with hospital data, a computerized system simulation model was designed. We analyze factors that may affect the total LOS in each hospital and categorize them as low, medium and high. Using the categorization, we demonstrate how the LOS may be improved through changes in clinical practice.
4. *Identify standardized processes in each hospital's protocols and compare the variation among them.* Some hospitals follow strict institutional protocols in managing patient care, while others employ flexible processes based on experience. As care process becomes more complex and involves different levels of providers, communication and role definition becomes more important. We study the existence of institutional standards and the compounded effects of protocols.

3.1.2 Method

Our study team, comprised of a pediatric cardiologist, a cardiac intensivist, a cardiac surgeon and a group of system engineers, completed week-long site visits to five pediatric heart centers, Children's Healthcare of Atlanta, Children's Healthcare of Philadelphia, C.S.

Mott Children's Hospital, Texas Children's Hospital and Primary Children's Hospital in Utah in 2012 and 2013.

Process and Workflow Observation and Data Collection

The site visits focused on observation and data collection of the entire operative and post-operative care process. Each site conducted their clinical tasks as usual and allowed the study team complete access to all events. We observed and recorded data and information in *OR process, hand-off from OR to ICU, care team resources and staffing in ICU, ICU rounds, ICU care process, chest closure in ICU, chest tubes removal in ICU, extubation in ICU, hand-off from ICU to CSU, and discharge coordination and family education in each hospital*. The observations focused on key factors including: 1) process and outcomes, 2) personnel and resource availability, and 3) decision making process. We captured activities from various personnel across the entire care continuum. Resource availability includes team composition, numbers of care members and skill set, staff shift and hours of care, and resource coordination and support for patient care. Decision making was noted throughout the post-op care process, including decisions pertaining to daily rounding, medications, sedations, laboratory test, x-ray, chest closure, tube removal, extubation, hand off from ICU to CSU, and discharge process.

Direct Interviews

We interviewed key personnel in four main areas: the patient-care team in ICU, the surgical team; the CSU and discharge team; and the administrative leaders. Specifically, the ICU personnel includes the *attending and fellow physician in the care team, nurse practitioner, respiratory therapist, pharmacist, nutritionist, charge nurse and registered nurse in ICU*. The surgical team covers the *attending and fellow surgeon, attending and fellow anesthesiologist, nurse practitioner, charge nurse, registered nurse, and physician assistant*. The CSU and discharge team personnel include *attending physician, charge*

nurse, registered nurse, social worker, and child life specialist if available. The administration leaders consists of *chief of cardiology, directors of ICU and CSU, chief of surgical team, head of nurse, director of research division, research physician and research nurse.* The interviews focused on key factors similar to those mentioned above pertaining to the direct observation and data collection processes. These include process and outcomes, resource availability, and the decision making process, By design, the observations and interviews allow us to correlate the actual processes and tasks that occur versus the perceived steps that the personnel follow.

Establish System Process Map

A patient care system process map is next created to help understand and analyze the interplay of care and coordination. Specifically, the pathway for patient care is first mapped out, following a patient from hand off from OR to ICU until discharge in each site. After identifying the patient care steps, key personnel who are involved with each patient care step and the available resources that support the task are overlayed onto the system process map. Next, decision making points and tasks are highlighted onto the system process map. Finally, we create an overall post-op care process common to all five sites from a systems viewpoint. Through the common system process map, variation points are captured and compared among the five sites. Figure 3-1 demonstrates the common post-operative process map.

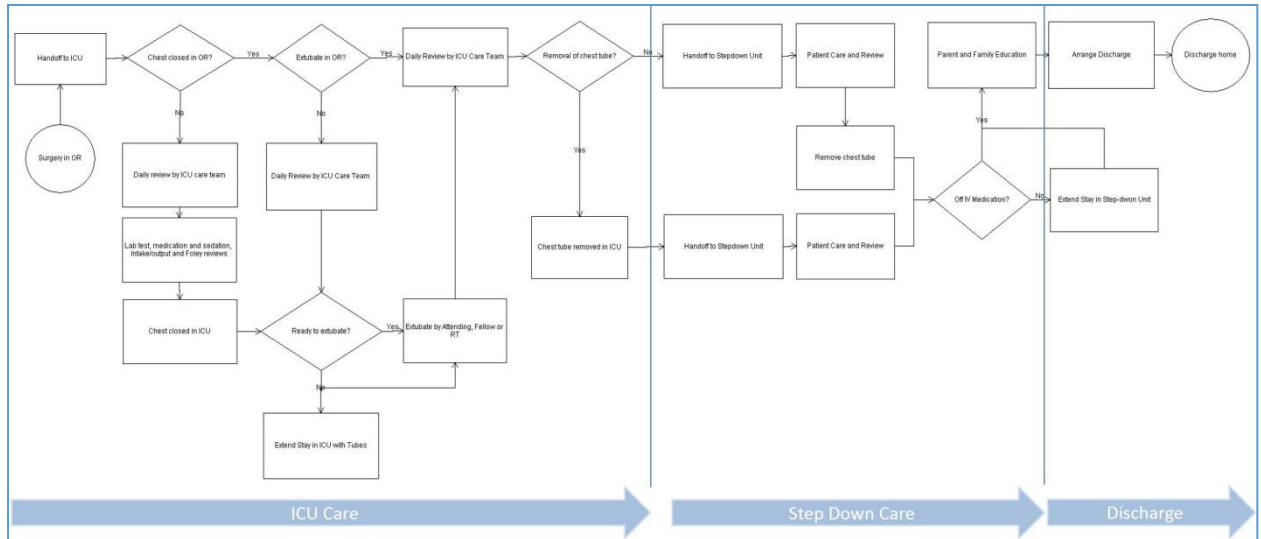


Figure 3- 1. A common post-operative process map for the five sites

Computer Systems Model, Machine Learning and Simulation

Combining observations and data from each hospital, we establish a computer system simulation model for further analysis. First we identify 7 major factors that influence LOS in each hospital:

- *Pre-Op*: Before surgery, patients usually stay in ICU for a day to prepare for surgery. We set this stage as Pre-op.
- *Surgery*: The length of surgery is between 2.5 hours to 6 hours.
- *Extubation*: Extubation may be performed in the OR after surgery. However, some patients may spend recovery time in the ICU and extubation is then performed in the ICU.
- *Tube removal*: This factor links to surgical care in the ICU. The surgical team may be involved in making the decision of removing the tubes and closing the chest. This step is complex and varied across the sites.
- *ICU care*: Patients recover in the ICU after surgery. The ICU care team takes care of the patients with care plan updated every day. Based on our observations, each hospital has a different approach in the creation of patient care plans.

- *Discharge planning*: Each hospital has its own family education plan and checklist. We focus on when and where each hospital begins the discharge and education plans.
- *Step-down care*: Patients move to step-down area for recovery. Step-down care is less intensive, nonetheless patients may spend extensive time in the step-down area.

To scope the study, the team decided to focus on two procedures: Tetralogy of Fallot (TOF) complete repair such as VSD (Ventricular septal defect) and ASD (atrial septal defect); and Coarctation of the Aorta (specifically < 12 month of age). Each center operates roughly 25 ~ 40 of these procedures per year. Variables are assigned the following distributions based on observations and discussions. Uniformly across each site, Pre-op takes approximately one day. Table 3-1 summarizes the distributions used for each of the factors at each site. “Tri” means triangular distribution and “N” means normal distribution. We caution that within the system simulation model, each entity is characterized not only by the service distribution; rather, the characteristics of the process, interplay of providers and processes and patients are all captured and simulated.

Table 3- 1. Summary of service time distribution for each of the factors at each site

	Pre-Op	Surgery	Extubation	Tube Removal	ICU Care	Discharge Planning	Step-down Care	LOS
Site 1	1	2.5 – 6 hr	0 ~ 3	0 ~ 2	2	~ 1	1.5	8
	Fixed		Tri(0, 1.2, 2.5)	Tri(0, 1.2, 2)	N(2, 0.25)	Tri(0.5, 0.8, 1)	Fixed	
Site 2	1	2.5 – 6 hr	0 ~ 1	0 ~ 1.5	1.5	~ 1	1	5
	Fixed		Tri(0, 0.3, 1)	Tri(0, 0.8, 1.5)	N(1.5, 0.25)	Tri(0.5, 0.8, 1)	Fixed	
Site 3	1	2.5 – 6 hr	1 ~ 4	0 ~ 5	3 ~ 6	~ 1	1.5	11
	Fixed		Tri(1, 2, 4)	Tri(0, 2.5, 5)	Tri(3, 3.5, 6)	Tri(0.2, 0.8, 1)	Fixed	
Site 4	1	2.5 – 6 hr	0 ~ 2	0 ~ 3	2 ~ 4	~ 2	2 ~ 4	14
	Fixed		Tri(0, 1, 2)	Tri(0, 1.5, 3)	Tri(2, 3.5, 4)	Tri(0.5, 1.5, 2)	Tri(2, 3, 4)	
Site 5	1	2.5 – 6 hr	0 ~ 1.5	0 ~ 2	1 ~ 2	~ 1	1 ~ 2	6
	Fixed		Tri(0, 0.8, 1.5)	Tri(0, 1.25, 2)	Tri(1, 1.25, 2)	Tri(0.5, 0.8, 1)	Tri(1, 1.2, 2)	

To understand the LOS correlation across the five sites, we first perform an expectation–maximization (EM) clustering algorithm on the surgical cases to categorize the LOS into related groups. Machine learning is then performed to pinpoint the key factors that are most predictive of the LOS. Based on the machine-learning results, we synthesize potential clinical strategy to reduce LOS. Simulation is then performed to analyze the potential improvement over the current practice.

3.1.3 Results and Findings

Based on our site visits, we identified numerous points of process variation and ample opportunities for process improvement in post-op care. We summarize below some of our findings.

ICU Care Process

All five sites have similar care teams for post-op care in ICU. Basically, ICU patient care is provided by two teams, each consisting of an attending physician, along with one or two fellows to cover the daytime shift. There are some variations. First, site 4 is unique in its care team formation compared to the other sites. Namely sites 1, 2, 3, and 5 have two teams in ICU with each team covering half of the ICU patients, while site 4 has one team consisting of two attendings and three to four fellows covering all ICU patients.

Table 3- 2. Number of beds at each of the five sites

	Site 1	Site 2	Site 3	Site 4	Site 5
# of beds	24 (Opens 20)	30	30 (Opens 18~20)	20	21

At site 2, only physicians perform morning rounds, whereas a pharmacist and a nutritionist participate along with physicians in the other four sites. In addition, site 2 care team takes much longer time at each bedside because the team performs medical actions such as extubation and ordering of medications during the morning rounds while the other four sites perform medical actions only after rounds are completed.

At sites 2 and 5, night shift patient care is covered by an attending and a fellow, whereas at the other 3 sites, only a fellow is present to cover the ICU night shift, attendings are available on call. As a result, various medical actions are made during the night shifts at sites 2 and 5; while the other 3 sites generally perform these medical actions in early morning when attendings are present.

Finally, only sites 2 and 5 perform collaborative joint rounds with specialists from other divisions for patients with complex disease. They join the ICU care team in the morning walking rounds, and discuss with the ICU team on the patient care plan every day. Table 3-3 summarizes practice variations across the ICU care process among the five sites.

Table 3- 3. Summary of practice variations in ICU care process

	Site 1	Site 2	Site 3	Site 4	Site 5
Care team Daytime shift	2 teams: each with 1 Attending 1 Fellow + PA(or NP) RT Pharmacist Nutritionist	2 teams: each with 1 Attending 2 Fellows	2 teams: each with 1 Attending 2 Fellows or 1 Fellow + NP Pharmacist Nutritionist	1 team with 2 Attendings 3 to 4 fellows Pharmacist Nutritionist	2 teams: each with 1 Attending 2 Fellows Pharmacist Nutritionist
Care team Night shift	1 ~ 2 Fellows with attending on call	1 Attending 2 Fellows	1 Fellow + NP with attending on call	2 Fellows with attending on call	1 Attending 1 Fellow

Table 3- 3. Continued

Joint rounds with specialists	No	Yes	No	No	Yes
Average time per patient	7 to 9 minutes	30 minutes	10 minutes	7 minutes	6 to 10 minute

Decision Making and Coordination

In daily post-op care, there is practice variation on patient care coordination and decision making processes. Each site has a different policy on a collaborative meeting between ICU team and surgical team. Sites 4 and 5 hold a joint meeting that includes both the ICU and the surgical teams every morning; while weekly meeting and seminar are observed at sites 1, 2, and 3. As a result, the surgical teams in sites 4 and 5 make decision on patient care plan and / or they are actively engaged in surgical action such as chest closure and chest tube removal; whereas such decisions usually are made by the ICU team at sites 1, 2, and 3. A surgical team member, usually a fellow surgeon, performs chest closure at sites 3 and 5; while ICU attending and fellow perform such a surgical care at sites 1, 2, and 4.

Additionally, decisions made during rounds show some variation. All sites except site 3 update patient care plans such as medications, ventilation setting, extubation schedule and feeding on a daily basis while the care team conducts walking rounds. On the other hand, site 3 handles the patient care plan very conservatively, it updates care plan after the ICU attending call.

For hand off, all sites employ a team-to-team approach. However, site 1 process is less structured than the other four sites. Typically, an attending anesthesiologist and a fellow surgeon and other OR staff move patients to ICU. However, only ICU attending and attending anesthesiologist are present during hand-off at site 1 while anesthesiologist and

fellow surgeon report patient information to the ICU team during hand-off at the other four sites.

For shift change, sites 3 and 5 change shift as team to team through the evening round, both daytime and night shift team members attend rounds and share information about the patients. Sites 1, 2, and 4 change shift via a process approach. Night shift team conducts the evening rounds without daytime shift team because they share information before evening rounds in a person-to-person meeting.

Except site 3, decision making of early extubation in the OR or extubation in the ICU within an hour after hand-off is made by attending anesthesiologist during the operation. In particular, site 2 and 4 are more proactively engaged in early extubation than the other sites. Meanwhile, site 3 does not perform early extubation in the OR. For extubation in the ICU, the attending physician decides when to extubate across all five sites, but the actual extubation is carried out with some difference. Attending physician generally performs extubation at sites 2 and 5 while one of the available personnel among attending, fellow, NP and RT performs extubation at the other sites.

Table 3-4 summarizes the practice variance on decision making and care coordination. It includes also comparisons on x-ray order, laboratory test order, sedation and feeding guideline.

Table 3- 4. Summary of practice variance in decision making and care coordination

	Site 1	Site 2	Site 3	Site 4	Site 5
Collaboration meeting between surgical and ICU teams	Weekly	Weekly	Weekly	Daily	Daily

Table 3- 4. Continued

Surgical decision maker in ICU	ICU team	ICU team	ICU team	ICU team and surgical team together	Surgical team
Surgical care in ICU	ICU team	ICU team	Surgical team	ICU team	Surgical team
Update care plan	Daily base	Daily base Patient's need base	Attending's call Conservative approach	Daily base	Daily base
Hand off from OR to ICU	Between attending anesthesiologist and attending physician	OR team to ICU team	OR team to ICU team	OR team to ICU team	OR team to ICU team
ICU team shift change	Process approach One to one	Process approach One to one	Team to team	Process approach One to one	Team to team
Early extubation	Yes by attending anesthesiologist	Yes by attending anesthesiologist	No	Yes by attending anesthesiologist	Yes by attending anesthesiologist
Extubation in ICU	Attending Fellow NP RT	By ICU attending	Attending Fellow NP RT	Attending Fellow NP RT	By ICU attending
X-ray order	Request basis	Request basis	Daily basis	Request basis	Request basis
Lab test	Daily basis	Daily basis	Daily basis	Daily basis	Patient's needs basis
Sedation	Attending's call	Avoid	Generous	Avoid	Attending's call
Feeding	Guideline	Daily basis	Guideline	Daily basis Guideline	Daily basis

Discharge Plan, Family Education and Protocols

Each hospital has a different approach for discharge and family education. Discharge plan begins in the ICU at sites 1, 2, 5; whereas it begins in the CSU for sites 3 and 4. All five sites provide medication and recovery education to family in the ICU; but most sites provide training in the CSU except site 2. Site 2 begins all family education in the ICU. Table 3-5 summarizes written document protocols based on observations and interviews.

Table 3- 5. Contrast of practice variations in discharge, family education and protocols

	Site 1	Site 2	Site 3	Site 4	Site 5
Discharge plan	ICU	ICU	CSU	CSU	ICU
Family education	Mostly CSU	ICU	Mostly CSU	Mostly CSU	Mostly CSU
Patient care protocols	Yes	No	No	No	Yes, but does not use it
Feeding protocols	Yes	No, experience basis	Yes, but just reference	Yes	Yes, but just reference
Ventilation protocols	Yes	No	Yes	No information	No
Sedation protocols	Yes	No information	Yes	Yes	No information
Discharge protocols	Checklist Guideline	Checklist Guideline	Guideline	Guideline	Checklist Guideline

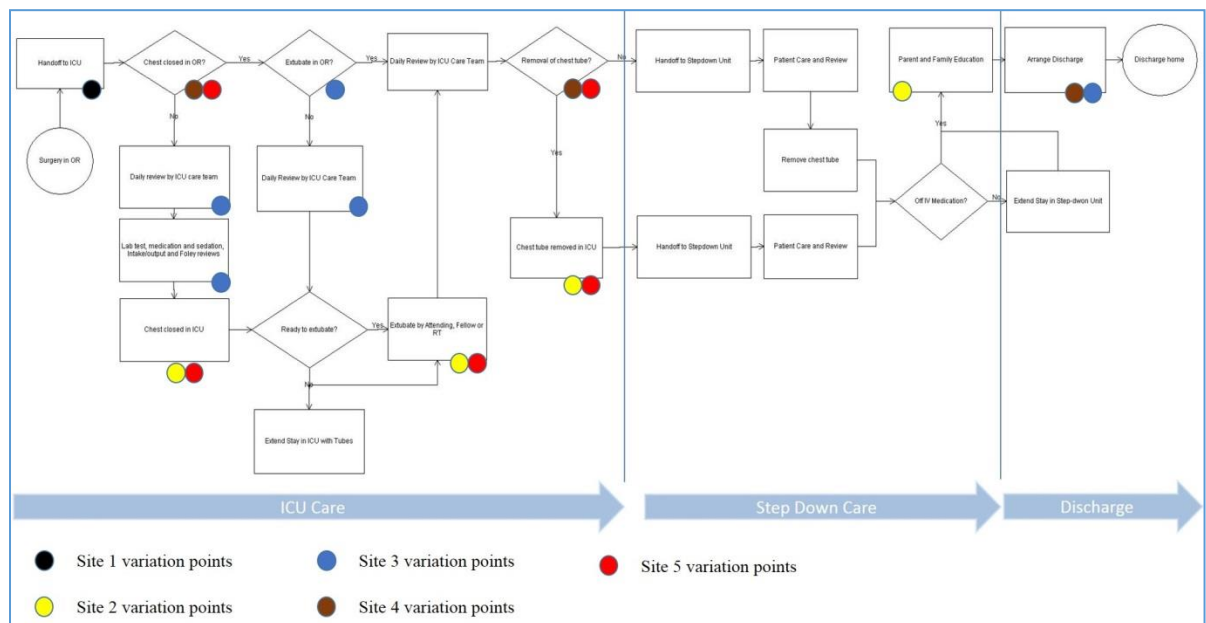


Figure 3- 2. Practice variance at each hospital

We highlight the following variance among the five sites on the process map.

- Hand-off from OR to ICU communications:* Site 1 uses one-to-one communication between OR attending anesthesiologist and ICU attending physician, while the other 4 sites use team-to-team communication.

- *Surgical decision in ICU:* In Sites 4 and 5, surgical team makes surgical care plans in ICU such as chest closure and tube removal, while ICU team makes the plans in the other 3 sites.
- *Surgical performer in ICU:* Interestingly, the surgical team performs chest closure and tube removal in site 2 and 5, while the ICU team performs the care in the other 3 sites.
- *Early extubation policy:* Site 3 does not have an early extubation policy, while the other 4 sites all have it.
- *ICU care plan:* At site 3, ICU team approaches daily care plan very conservatively, sometime completely depending on ICU attending's call. While the other 4 sites update the plan aggressively.
- *Extubation in ICU:* ICU attending physicians mainly perform the extubation at sites 2 and 5, while available staff such as fellow physician, nurse practitioner or respiratory therapist can perform the extubation based on attending's call in the other 3 sites.
- *Family education:* Family education begins at ICU in site 2, while it begins at CSU in other 4 sites.
- *Discharge plan:* Discharge plan begins at ICU at sites 1, 2 and 5, while it begins at CSU at sites 3 and 4.

Lastly, we observed a difference in process order among the 5 sites. In Figure 3-3, we include 9 important steps for post-op processes and their sequences in each hospital.

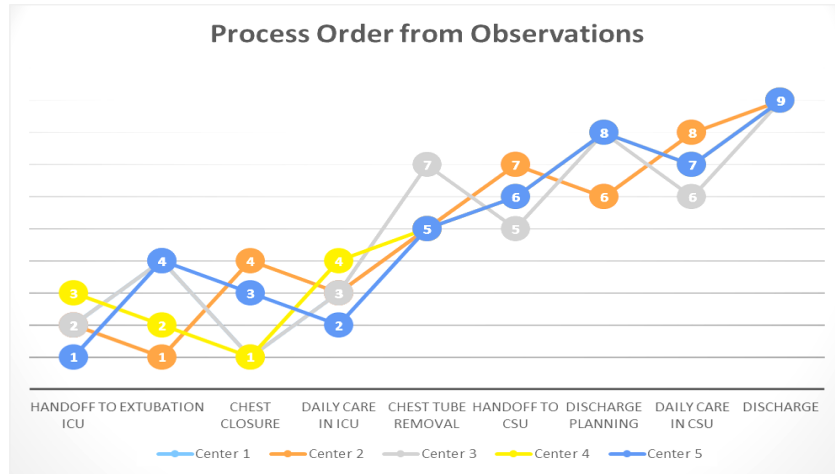


Figure 3- 3. Process order in each hospital

EM Clustering, Machine Learning and Simulation

EM clustering performed on the surgical cases of the five sites yield three distinct clusters based on the LOS: *Short*: $LOS \leq 6.7$, *Medium*: $6.7 < LOS \leq 8.8$, *Long*: $LOS > 8.8$ (Figure 3-4). The distribution is roughly 31.2%, 26.7%, and 42.0% respectively.

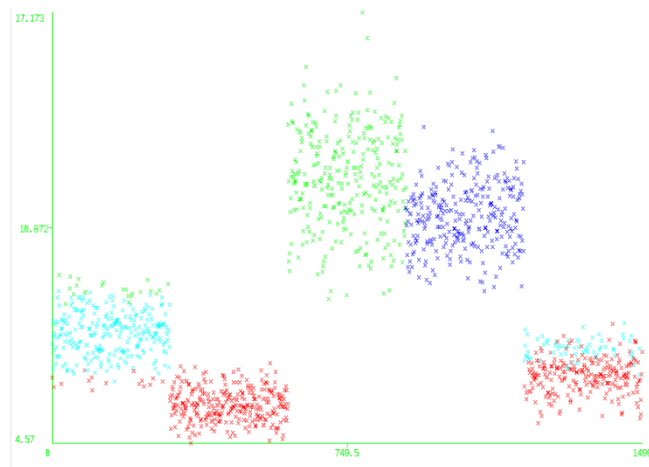


Figure 3- 4. Clusters of LOS from the five sites

We select randomly 66% of these surgical cases and perform supervised learning on them using 24 different types of classifiers, including DAMIP[79, 85], logistic model decision tree, random forest, support vector machine, naive Bayesian, k-nearest neighbors,

and Bayesian network. The remaining 34% of surgical cases are used for blind prediction. DAMIP performs the best with 95% 10-fold cross-validation unbiased estimate, and over 90% on blind prediction accuracy for each of the 3 groups. Bayesian network also returns excellent results with 92.8% 10-fold cross-validation unbiased estimate, and over 85% blind prediction accuracy for each of the groups. All other classifiers suffer from imbalanced data and score unevenly in one of the group prediction.

Running feature selections on the 7 major factors on all the classifiers, we select the top 50 percent of all the models and calculate the Gini Importance on the features to determine their significance in predicting/influencing the LOS. Table 3-6 shows that ICU, step-down, and early extubation are the top three features. ICU and step-down care are complicated factors as they involve multiple resources, staffing, medication and care coordination, and scheduling among various units in the hospital. Meanwhile, extubation is a process that the hospital can conveniently adopt a new protocol and measure its impacts on LOS. Furthermore, extubation can affect time it takes for tube removal and ICU care management simultaneously, and will have a downstream effect on step-down care also.

Table 3- 6. The Gini Importance score for each of the factors in predicting the LOS

Factor	Extubation	Tube Removal	ICU care	Stepdown care	Discharge Plan
Total Gini Importance Score	82	72	89	93	70

We first run the computer system simulation model using the 7 major factors collected from field observations and the parameters in Table 1 to arrive at the expected LOS of each hospital. Next, we simulate early extubation to estimate the expected improvement in LOS. Figure 3-5 contrasts the results. In particular, “simulation observations” reports the simulation results of the current LOS based on our field observations, while “simulation early extubation” reports the anticipated LOS when early

extubation is implemented at each site. We find significant reduction in LOS, ranging from 10.0% to 30.0%. This may have significant impact on the health and cognitive development of the patients.

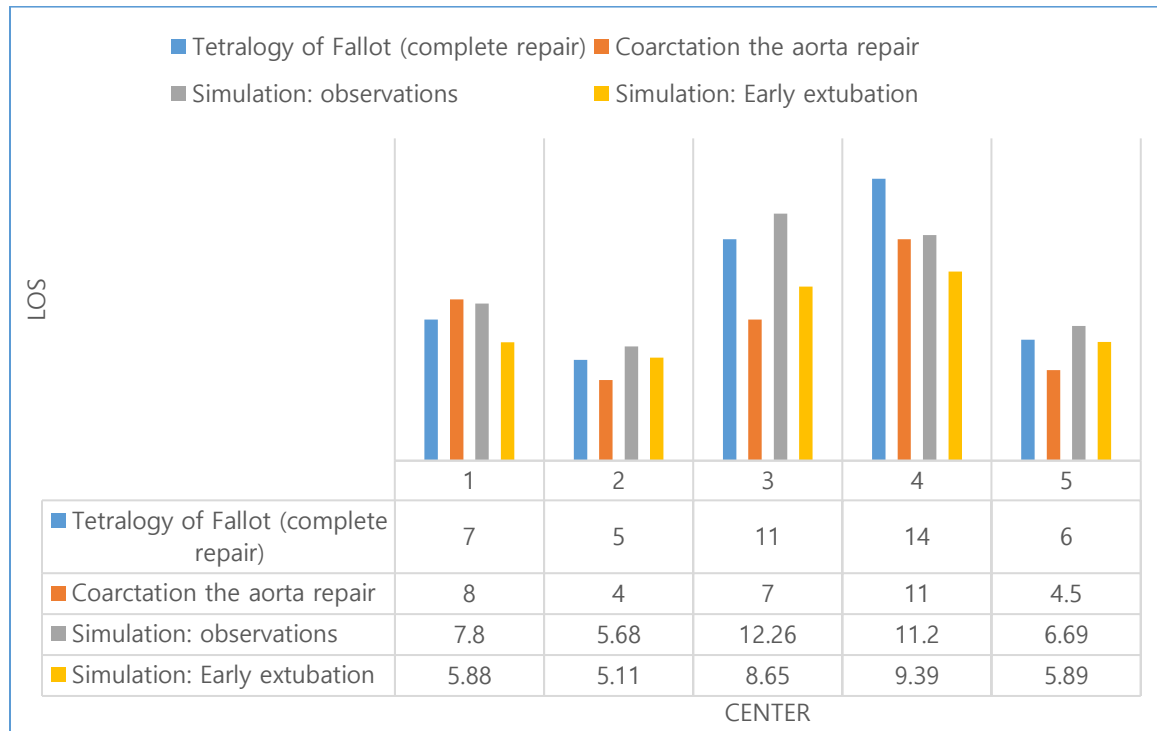


Figure 3- 5. Comparison of LOS statistics

3.1.4 Discussion

This paper focuses on understanding and analyzing patient care process variation in post-operative care of congenital heart surgery. We aim to identify practice variance and the associated processes and/or factors that may offer opportunities for improving care delivery and clinical outcome. Focusing on five pediatric heart surgery sites, we have identified and summarized numerous practice variations within the post-operative care process. Specifically, from a system viewpoint, we pinpoint various process points along the post-op care continuum in which difference in care coordination, management, resources and

practice may lead to significant impact and reasons for the difference in LOS across the five sites.

Using clustering and machine learning approaches, we rank the significance of these factors in predicting and influencing the length of stay of the patients. In particular, ICU care, step-down care, and early extubation offer the highest potential of returns. The strength of this study is that by combining direct observations and data collecting, interviews, system process map design, system simulation, and machine learning together, we can *identify* and *prioritize* major practice variance and key factors that may influence clinical outcome. The findings can be readily presented in a systematic manner to the hospitals for potential process improvement.

Although analysis of multi-institutional information might provide insight about such practice variation, the process is time-consuming and study design is not trivial. It is difficult to capture critical factors that may enhance patient care such as decision-making processes, information transfer, and the use of protocols.

Each site may apply our findings to identify its own weakness and potential improvement of its current process. The findings may assist clinicians in developing clinical practice guidelines and protocols for improving LOS and treatment outcome. While LOS is only one measure of outcome, it may have significant impact.

Beyond individual site improvement, this work facilitates collaborative learning across the multi-institutional sites. ICU and step-down care are complicated factors as they involve multiple resources, staffing, medication and care coordination, and scheduling among various units in the hospital.

Because changes in ICU and stepdown care can be complex and involve multiple staff, and process change and care coordination and scheduling involving numerous units at multiple timeline within the care process, early extubation offers a unique opportunity for collaborative learning. Multi-site testing of a change process is important for clinical improvement and in validating effects from change in clinical practice when the number of surgical cases at each site is not high. At the time of this writing, a collaborative learning study has been started with a new clinical practice guideline (CPG) established for early extubation for a selected group of patients. A clinical trial involving these five sites, using the new CPG, began in April 2014. A clinical paper is currently in preparation to discuss the design of the collaborative study and the establishment of the CPG protocol.

The findings in this study allow us to better understand patient workflow and care processes for pediatric heart patients. Besides early extubation, we will explore areas of potential improvement based on our findings. In particular, we will identify actionable changes that can be tested to understand the impact on LOS and the clinical outcome for the patients. Such work requires careful design of CPG and implementation protocol, and clinical trials must be carried out to understand potential impacts and effects.

Acknowledgment

This work is partially supported by a grant from the National Science Foundation and the National Institutes of Health.

3.2 Investigating a Needle-Based Epidural Procedure in Obstetric Anesthesia

This section consists of the entire paper, “Investigating a Needle-Based Epidural Procedure in Obstetric Anesthesia” that has been submitted to *Anesthesiology*.

Investigating a Needle-Based Epidural Procedure in Obstetric Anesthesia

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Abstract

This paper reports the findings of an investigation into the safety and efficacy of a new large-dose, needle-based epidural technique in obstetric anesthesia. The new technique differs from a traditional, catheter-based approach in that the anesthetic dose is administered through an epidural needle prior to insertion of the epidural catheter.

Two cohorts of subjects supplied data: the first composed of 750 patients permitted modeling and predictive analysis; the second that included 1,398 randomly selected patients provided independent validation.

The study revealed that, compared with a catheter-based approach, a needle-based approach is faster (mean 15.63minutes versus 20.00 minutes) and more dose-effective (mean 24.99 ml versus 30.27 ml) in achieving comparable sensory levels. The study also showed that injecting large doses (up to 20 ml) in the epidural space through the epidural needle is safe, followed usually by good outcomes for patients; any associated complications were similar to those reported in published literature. Further, we found that if the needle dose is kept under 18 ml the resulting hypotension rate ordinarily will be significantly lower (mean 21%).

Using advanced analytics, we developed a machine learning framework that can predict the incidence of hypotension with 85% accuracy. The discriminatory features uncovered

include weeks of pregnancy, patient allergies, number of epidural replacements, epidural needle/catheter dose, number of epidural reboluses and dosage).

The findings from this investigation should facilitate delivery improvement as well as help establish a revised guideline for training and for dissemination of best practice.

3.2.1 Introduction

The potential consequences of failed or misplaced epidural needles are well known to obstetric anesthesiologists. A well-documented epidural complication, a “wet tap,” results in a headache and possible total spinal, requiring immediate maintenance of the patient’s airway and blood pressure. The inadvertent intravenous injection of local anesthetic into a vein in the epidural space leads to seizures and fatal cardiac arrhythmias. Equally worrisome is the inadequate epidural block leading to complications during a caesarian section. These complications include an emergency general anesthetic, resulting in airway loss, hypoxemia, hypercarbia and death[86-88]. However, to date, limited research has been performed regarding standardization of the epidural analgesia procedure to avoid practice variance with minimal complications. Furthermore, little is known regarding practice and patient outcome related to large doses of local anesthetic injected through the epidural needle.

In this paper, we perform an in-depth study of epidural process to capture practice variance and to quantify the time and dose required to achieve the desired sensory level. In particular, we establish a safe and quickly effective epidural dose that can be administered through the epidural needle prior to the insertion of the epidural catheter. Based on clinical results, we quantify complications for doses as large as 20 ml that is injected through the epidural needle. We contrast the proficiency of physician practice and provide insights on

their preference in medication and dosage. Understanding the causes and effects of such variation can help providers and healthcare organizations avoid practices that negatively impact outcomes. Using machine learning approach, our study reveals practice characteristics that result in the best outcome with least complications. Our findings facilitate establishment of new clinical practice guidelines (CPG) for care outcome and delivery improvement.

3.2.2 Materials and Methods

This study aims to capture practice variance, quantify dose-sensory achievement characteristics, and evaluate the safety and utility of injecting large doses (up to 20 ml) in the epidural space through the epidural needle for elective caesarian sections in the hands of experienced anesthesiologists at a large urban obstetric hospital. The study involves six major steps.

1. Develop process mapping of patient and epidural service workflow via objective process observations and structured interviews.
2. Perform time-motion studies of epidural processes, record complications and practice variance, and analyze hospital data.
3. Perform statistical analysis of collected data, conduct system analysis on practice variance, quantify effective dose-sensory level achievement, and develop a machine-learning predictive analytic to predict patient/outcome characteristics.
4. Develop a computerized simulation-optimization system to simulate current performance, optimize systems and estimate anticipated global improvement.
5. Report findings and determine practice guideline recommendations for improved quality of care.

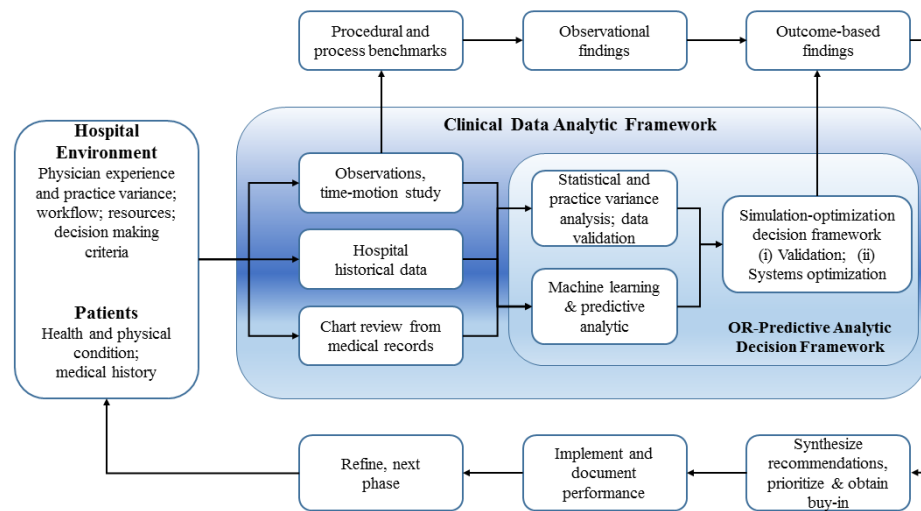


Figure 3- 6. The study schema and interdependencies of the analytic framework

Epidural Workflow and Services

Figure 3-7 summarizes the epidural process performed by anesthesiologists. We observe variation in the processes (green). Anesthesiologists choose one of three basic techniques (or a combination thereof) in order to correctly identify the epidural space via the technique of loss of resistance: air, saline and local anesthetic. Medication dosages vary by provider with the majority of them injecting as much as 20 ml's through the epidural needle prior to the insertion of the epidural catheter.

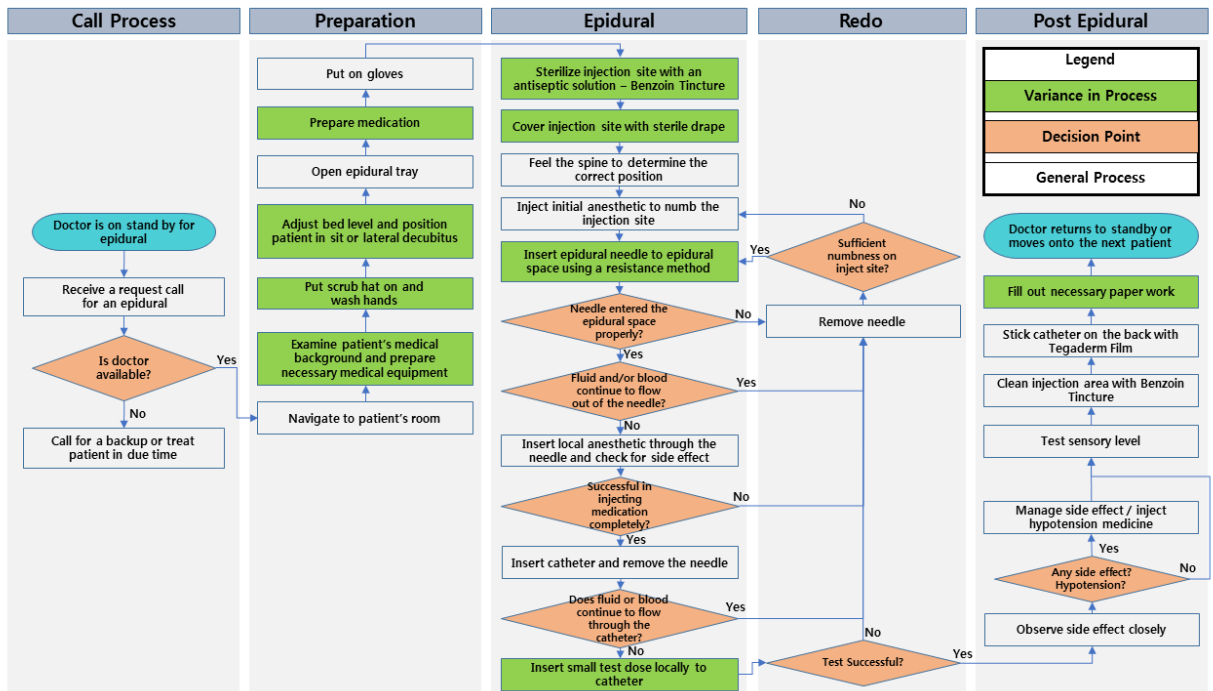


Figure 3- 7. Anesthesiologist epidural procedure workflow process. Green highlights processes with variance among providers

Observations, Time-Motion Studies, and Chart Review

From January 2014 through December 2014, eight trained observers collected epidural process data via a standardized checklist through shadowing the epidural team. Data collection included patient demographics, vital signs, medication type and dosage, time to achieve sensory level, outcomes and response to medication. The observers simultaneously conducted time-motion studies, measuring service time for each step of the epidural workflow. Variability of practitioners and processes were also captured. Along with observation, a random sampling of charts was reviewed to serve as a validation set for our machine learning and system simulation-optimization analysis.

Two types of epidural approaches were defined based upon the primary delivery mechanism of the majority dose. If the majority of the dose is delivered through a needle,

it is defined as a *needle-based* approach. Likewise, a *catheter-based* approach delivers the primary dose through a catheter.

Statistical Analysis

Statistical analysis was conducted to quantify variations and their associated outcome. Specifically, variations on delivery types, complications caused by delivery types, time to sensory level, medications and dosage, epidural approaches (needle-based and catheter-based), and practitioners' performance were noted.

Statistical analyses were performed using MATLAB[89]. Statistical significance was assessed at the 0.05 level unless otherwise noted. Descriptive statistics were calculated for all variables of interest and included: median and 25th to 75th percentiles, and counts and percentages, when appropriate. Two-sample t-test and Wilcoxon rank-sum tests were used to compare continuous variables between groups and Chi-square tests were used for comparing categorical variables between groups.

Next, a machine learning predictive framework was designed to uncover key factors influencing and predicting hypotension. Specifically, we used discriminant analysis via mixed integer program (DAMIP) as our classifier[85, 90] and contrasted it with other popular classification methods.

Machine-Learning Predictive Analytic Framework: Discriminant Analysis via Mixed Integer Program (DAMIP)

Suppose we have n entities from K groups with m features. Let $\mathcal{G} = \{1, 2, \dots, K\}$ be the group index set, $\mathcal{O} = \{1, 2, \dots, n\}$ be the entity index set, and $\mathcal{F} = \{1, 2, \dots, m\}$ be the feature index set. Also, let $\mathcal{O}_k, k \in \mathcal{G}$ and $\mathcal{O}_k \subseteq \mathcal{O}$, be the entity set which belong to group k . Moreover, let $\mathcal{F}_j, j \in \mathcal{F}$, be the domain of feature j , which could be the space of real,

integer, or binary values. The i th entity, $i \in \mathcal{O}$, is represented as $(y_i, \mathbf{x}_i) = (y_i, x_{i1}, \dots, x_{im}) \in \mathcal{G} \times \mathcal{F}_1 \times \dots \times \mathcal{F}_m$, where y_i is the group to which entity i belongs, and (x_{i1}, \dots, x_{im}) is the feature vector of entity i . The classification model finds a function $f: (\mathcal{F}_1 \times \dots \times \mathcal{F}_m) \rightarrow \mathcal{G}$ to classify entities into groups based on a selected set of features.

Let π_k be the prior probability of group k and $f_k(\mathbf{x})$ be the conditional probability density function for the entity $\mathbf{x} \in \mathbb{R}^m$ of group k , $k \in \mathcal{G}$. Also let $\alpha_{hk} \in (0,1)$, $h, k \in \mathcal{G}, h \neq k$, be the upperbound for the misclassification percentage that group h entities are misclassified into group k . DAMIP seeks a partition $\{P_0, P_1, \dots, P_K\}$ of \mathbb{R}^K , where P_k , $k \in \mathcal{G}$, is the region for group k , and P_0 is the reserved judgement region with entities for which group assignment are reserved (for potential further exploration).

Let u_{ki} be the binary variable to denote if entity i is classified to group k or not. Mathematically, DAMIP[85, 91-93] can be formulated as

$$\text{Max } \sum_{i \in \mathcal{O}} u_{y_i i} \quad (1)$$

$$\text{s.t. } L_{ki} = \pi_k f_k(\mathbf{x}_i) - \sum_{h \in \mathcal{G}, h \neq k} f_h(\mathbf{x}_i) \lambda_{hk} \quad \forall i \in \mathcal{O}, \quad (2)$$

$$u_{ki} = \begin{cases} 1 & \text{if } k = \arg \max\{0, L_{hi} : h \in \mathcal{G}\} \\ 0 & \text{otherwise} \end{cases} \quad \forall i \in \mathcal{O}, k \in \{0\} \cup \mathcal{G} \quad (3)$$

$$\sum_{k \in \{0\} \cup \mathcal{G}} u_{ki} = 1 \quad \forall i \in \mathcal{O} \quad (4)$$

$$\sum_{i: i \in \mathcal{O}_h} u_{ki} \leq \lfloor \alpha_{hk} n_h \rfloor \quad \forall h, k \in \mathcal{G}, h \neq k \quad (5)$$

$$u_{ki} \in \{0, 1\} \quad \forall i \in \mathcal{O}, k \in \{0\} \cup \mathcal{G}$$

L_{ki} unrestricted in sign

$$\forall i \in \mathcal{O}, k \in \mathcal{G}$$

$$\lambda_{hk} \geq 0$$

$$\forall h, k \in \mathcal{G}, h \neq k$$

DAMIP has many appealing characteristics including: 1) the resulting classification rule is *strongly universally consistent*, given that the Bayes optimal rule for classification is known[94, 95], 2) the misclassification rates using the DAMIP method are consistently lower than other classification approaches in both simulated data and real-world data; 3) the classification rules from DAMIP appear to be insensitive to the specification of prior probabilities, yet capable of reducing misclassification rates when the number of training entities from each group is different; 4) the DAMIP model generates stable classification rules on imbalanced data, regardless of the proportions of training entities from each group[90, 94, 96].

The entities in this study correspond to the patients. The features are patient demographics, health conditions and clinical history, epidural workflow (processes, medication, and dosage), and provider experience and delivery characteristics. The goal is to uncover discriminatory features that can predict which patients will have a higher likelihood for complications. Identifying these patients will allow practitioners the chance of intervening with the intention of reducing complications. It also facilitates development of new CPGs for improved clinical outcome.

In supervised learning, each subject's status in the training set is known. The training data are input into the DAMIP machine-learning framework. Ten-fold cross-validation is performed on the training set to obtain an unbiased estimate.

In 10-fold cross-validation, the training set is randomly partitioned into 10 roughly equal subsets. Of the 10 subsets, 9 subsets are used as training data, and the remaining 1

subset is retained as the validation data for testing the rule. The cross-validation process is then repeated 10 times (the folds), with each of the 10 subsets used exactly once as the validation data. The 10 results from the folds are then summed to produce an unbiased estimation. The advantage of this method over repeated random subsampling is that all entities are used for both training and validation, with each entity used exactly once for validation.

To gauge the predictive power of the rule, we perform blind prediction on an independent set of subjects; that is, these individuals have never been used in the learning process. We run each subject through the rule, which returns a status. This status is checked against the individual's actual status. Hence, we always compare our prediction with the actual outcome in measuring predictive accuracy.

Lee et al.[91] (2003), Lee[85] (2007a), Lee and Wu[92] (2009), Brooks and Lee[94] (2010), and Brooks and Lee[95] (2014) detail the DAMIP modeling and its theoretical and computational contributions. Note that mathematically DAMIP is proven to be *NP-complete*[94, 95]. We solved the instances for this epidural study using advances in hypergraphic theory[97].

Development of a Computerized Simulation-Optimization System

A computer simulation-optimization model was established as a framework for modeling and optimizing the entire epidural workflow. This allows for development of improved CPGs.

Parameters in the simulation include the entire epidural workflow as shown in Figure 2. The model captures delivery characteristics, service time, types and probabilities for each provider; response, risk factors, and outcome characteristics (including

complication) of each patient; and overall throughput of processes. The model was fitted using the data collected from our time-motion studies and observations to simulate the annual hospital patient visits and treatment performance. The computer simulation model captures practice variations statistically, and allows us to investigate improvement strategies. We first fine-tuned the model to reflect the hospital regular performance. Then using the validation set from chart review, we further fine-tuned and cross-validate the accuracy of our model. The system was then optimized to identify areas of improvement.

3.2.3 Results

Northside Hospital delivers the highest number of newborns in the United States (the Centers for Medicare & Medicaid Services). During the study period, 19,651 deliveries were performed with 55.3% vaginal birth and 44.7% C-section. Among these, 75.1% received epidural analgesia. A total 750 parturition cases under routine epidural analgesia were observed in full detail. This includes 667 C-section, 76 vaginal birth, and 7 unlabeled cases. Majority of them (94%) were performed with patients in the sitting position. The observations cover 44 anesthesiologists.

The two groups of patients have similar distributions in weight ($p < 0.3138$), height ($p < 0.5784$), and weeks of pregnancy ($p < 0.3082$). The occurrence of allergies is similar (C-section group: 13.75%, vaginal birth group: 16.44%). 73.04% of the C-section patients have had previous deliveries. And, 29.41% of the vaginal deliveries are primigravidas. The systolic blood pressure of C-section and vaginal birth patients is similar ($p < 0.5700$). However, the diastolic pressure of vaginal birth patients (73.0714 mmHg) is lower than that of the C-section patients (78.0315 mmHg) ($p < 0.0074$).

The independent set of patients used for validation of findings consists of 1,398 cases obtained through chart review. This includes 892 C-section, 505 vaginal births, and 1 unlabeled case. This represents 10% of the newborns between January to September 2015.

C-section versus Vaginal Birth

Table 3-7 compares vaginal birth and C-section by age, type of medication and dosage, time to achieve desired sensory level, achieved sensory level, and outcomes.

Age: It is well-documented that advancing maternal aged women are more likely to have cesarean delivery without labor[98]. The hospital data echoed this trend. The average age for the C-section group was 32.72 versus 30.77 of the vaginal birth group (p -value < 0.0089).

Medication: More than 40 combinations of medication are used. Table 3-7 shows the most commonly used drug combinations. Ropivacaine is used for vaginal birth patients since Ropivacaine is less lipophilic than bupivacaine and less likely to penetrate large myelinated motor fibers, resulting in a relatively reduced motor blockade. It is preferred in vaginal birth where motor blockage is undesirable[99].

Sensory level achievement: Sensory level is an important indicator to measure the effect of anesthesia. A higher than desired anesthesia level (high block) can cause motor block, dyspnea, apnea and even loss of consciousness. Both groups achieve similar sensory level, with T4 and T6 being the most frequently achieved. However, the time it takes to achieve sensory level between the vaginal birth and the C-section groups is significantly different. The average time was 13.51 minutes versus 15.95 minutes respectively ($p < 0.0126$).

Complications: Our observations identified six complication symptoms: hypotension, epidural replacement, wet tap, blood in the catheter/needle, high block, and nausea and vomiting. Only two symptoms of complications, hypotension and blood in the catheter/needle, were observed in the vaginal birth group. Since hypotension is the most common complication, we present detailed analysis on hypotension in a dedicated section.

Table 3- 7. Variance between the vaginal birth and C-section patients

Field	Vaginal birth group		C-section		P-value*
Age	Min	18	Min	17	
	Q1	26	Q1	30	
	Median	31	Median	33	
	Q3	36	Q3	36	
	Max	39	Max	49	
	Mean	30.77	Mean	32.72	0.0089
	Mode	26	Mode	31	
Most Used Medications (Frequency)	Lidocaine 2%, NaHCO ₃ , Epinephrine, Fentanyl	15.58%	Lidocaine 2%, NaHCO ₃ , Epinephrine, Fentanyl	28.98%	
	Lidocaine 1.5%, Ropivacaine 0.5%, Epinephrine	14.29%	Lidocaine 2%, NaHCO ₃ , Epinephrine	20.23%	
	Lidocaine 2%, NaHCO ₃ , Epinephrine	11.69%	Lidocaine 2%, Epinephrine, Fentanyl	8.90%	
	Ropivacaine 0.5%	11.69%	Lidocaine 2%, Epinephrine	8.61%	
	Lidocaine 2%, Epinephrine	10.39%	Marcaine 0.5%, Fentanyl	5.74%	
Average Time to Sensory Level	13.51 minutes		15.95 minutes		0.0126
Achieved Sensory Level (Frequency)	T2	0.00%	T2	0.76%	
	T3	0.00%	T3	1.83%	
	T4	61.02%	T4	61.07%	
	T5	11.86%	T5	6.72%	
	T6	23.73%	T6	22.29%	
	T7	0.00%	T7	1.07%	
	T8	0.00%	T8	3.97%	
	T9	0.00%	T9	0.76%	
	T10	1.69%	T10	1.22%	
	T11	0.00%	T11	0.00%	
	T12	1.69%	T12	0.31%	

Table 3- 7. Continued

Complications (Frequency)	No complications	85.53%	No complications	40.93%
	*Hypotension	11.84%	*Hypotension	52.32%
	Blood in the catheter/needle	2.63%	Blood in the catheter/needle	2.10%
			Epidural replaced	3.60%
			Wet tap	0.15%
			High block	0.30%
			Nausea/Vomit	0.45%

*Documented by physicians as hypotension based on their own criteria.

Needle-based vs Catheter-based Approach

We seek to quantify effective dose to achieve desired sensory level and evaluate the safety and utility of injecting large doses (up to 20 ml's) in the epidural space through the epidural needle.

Among the 750 observed cases, 717 cases (95.6%) were needle-based and 33 cases (4.4%) were catheter-based. Table 3-8 shows the dose distribution across the two approaches. In the needle-based approach, in almost all cases over 90% of the dose is delivered through the needle; whereas for the catheter-based approach, an average of 60% of dose is delivered via the catheter.

Table 3- 8. Dose injected through needle and catheter for needle-based versus catheter-based

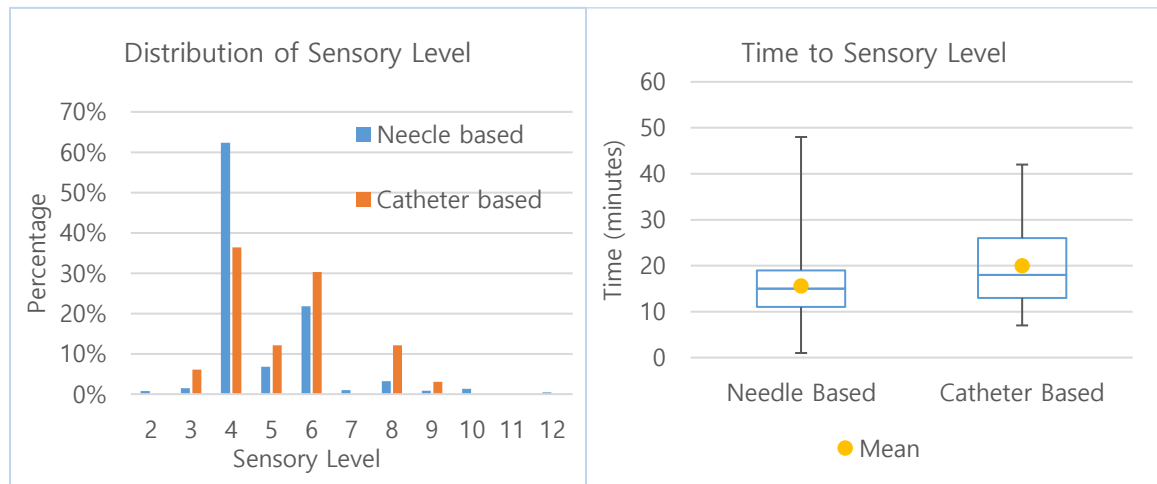
	Needle-based		Catheter-based	
	Dose through Needle	Dose through Catheter	Dose through Needle	Dose through Catheter
Min (ml)	5	0	2	10
Q1 (ml)	16	0	7.5	10
Median (ml)	20	0	10	10
Q3 (ml)	20	0	10	19.5
Max (ml)	32	18	20	28

Table 3- 8. Continued

Mean (ml)	18.66	1.42	9.70	13.97
Mode (ml)	20	0	10	10

Sensory level achievement: The average time to achieve similar sensory level ($p < 0.7789$) in needle-based approach was 15.63 minutes versus 20.00 minutes for catheter-based ($p < 0.0037$, Figure 3-8). The time difference is significant for both vaginal birth and C-section deliveries ($p < 0.0181$, $p < 0.0390$ respectively, Figure 3-9). *Hence, this study reports that needle-based approach is faster and effective in achieving the required sensory result.*

Furthermore, the needle-based approach uses less dose than catheter-based approach (mean 24.99 ml versus 30.27 ml, $p < 6.0 \text{ e-}05$, Figure 3-10). *These findings support that needle-based approach is more dose-effective, achieving faster and comparable sensory level as the traditional catheter-based approach.*

**Figure 3- 8. Needle-based vs Catheter-based: achieving comparable sensory level**

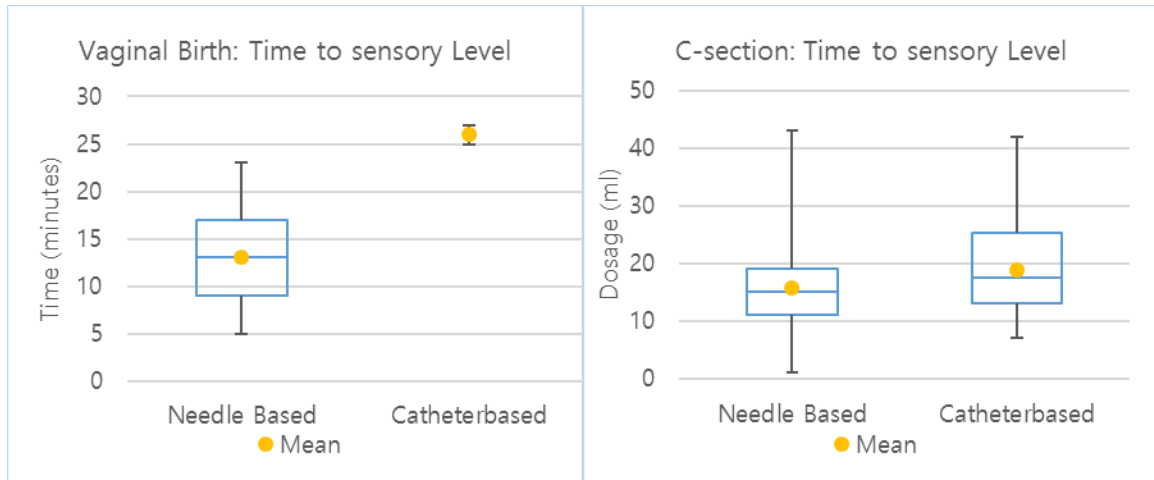


Figure 3- 9. Needle-based vs Catheter-based: time to sensory level in delivery types

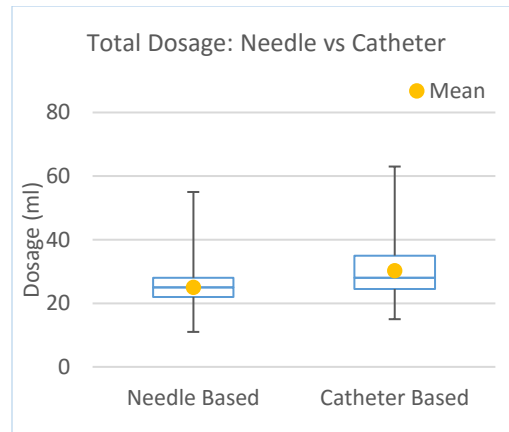


Figure 3- 10. Needle-based vs Catheter-based: epidural dose used

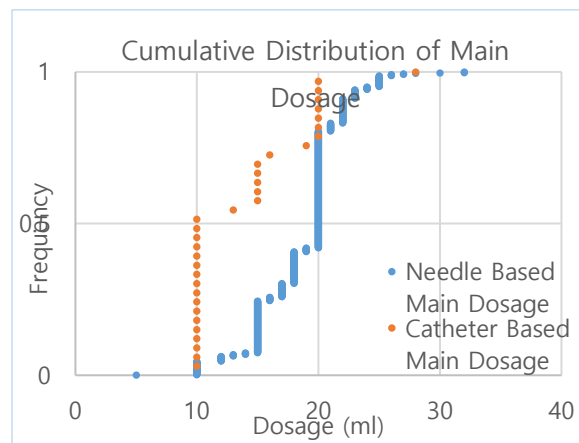


Figure 3- 11. Cumulative distribution of main epidural dose among 44 practitioners

Complications

General Statistics: Table 3-9 contrasts the hospital's incidence of complications to published results[100-111]. *Compared to published results, the complication incidence of needle-based approach appears to be comparable to traditional catheter-based approach.*

Table 3- 9. The hospital's complication rate against published results

Type of Complications	Epidural replace	Nausea/Vomit	Wet tap	High Block	Blood in the catheter/needle	Re-do local anesthetic	Re-do loss of resistance
Literature	4.7% - 17.8% (n=181–10995) [100-105]	1% (n=388) [106]	0.43% - 3.2% (n=141-29749) [100-103, 105-110]	0.02%-0.07% (n=10995-145550) [101, 111]	N/A	N/A	N/A
This study observed cases (n=750)	3.20%	0.40%	0.13%	0.27%	2.13%	4.00%	6.53%
This study: needle-based (n=717)	3.07%	0.42%	0.00%	0.28%	1.81%	4.04%	6.56%
This study: catheter-based (n=33)	6.06%	0.00%	3.03%	0.00%	9.09%	3.03%	6.06%

Hypotension: The most observed complications for spinal, epidural and combined spinal and epidural anesthesia (CSE), is hypotension. Depending upon different labor analgesia methods, hypotension rates reported by previous studies can be as high as 70% [112, 113]. Based on our practitioners' definition of hypotension, the hypotension rate was 51.73% across all approaches and delivery types. It was 52.32% for C-section and 11.54% for vaginal birth. And the average age of hypotension group was 33 and non-hypotension group was 32.0 ($p < 0.034$).

We apply published hypotension definitions to our study and compare the hypotension rates in Table 3-10. Since all previously reported results except one involved very small sample sizes, we can only meaningfully compare the hypotension results based on the “30% Drop of mean arterial pressure (MAP)” definition. Table 3-10 reports first the complication statistics for the observed cases. In the reporting, we do not separate the needle-based versus catheter-based cases since statistically, there is no significant difference in resulting percentage of hypotension. To validate that the observed cases are representative of the overall hospital practice, we also report the complication statistics for the 1,398 charts reviewed. *The study reveals that the needle-based approach requires less dose for faster and effective epidural analgesia without increasing the incidence of hypotension.*

Table 3- 10. Comparison of hypotension rates

	Percentage and sample size from literature		Percentage and sample size in our study					
			Observed cases			Chart Review cases		
	Vaginal birth	C-section n=107*	Vaginal birth n=76	C-section n=667	Overall n=750	Vaginal birth n=505	C-section n=892	Overall n=1398
<90 mm Hg, systolic	23.1% , n = 65[114]; 4.0%, n=375[106]	16.3%[115]	17.04%	23.73%	21.62%	13.86%	23.54%	20.03%
<90 mm Hg or a 20% decrease from baseline, systolic	0%, n = 40[116]; 5.2%, n=19[117]	54.8%[115]	35.37%	48.91%	44.64%	33.07%	48.65%	42.99%
<100 mm Hg	7.5%, n=375[106];	41.5%[115]	39.87%	50.66%	47.35%	38.22%	50.56%	46.14%
<100 mm Hg or >20% reduction from baseline, systolic	24%, n = 25[118]; 48% n=25[119]	59.3%[115]	49.20%	60.99%	57.36%	47.72%	60.65%	56.01%

Table 3- 10. Continued

<100 mm Hg or >30% reduction from baseline, systolic	9%, n = 53[120]	46.7%[115]	40.51%	53.42%	49.45%	39.21%	53.14%	48.14%
30% Drop of MAP	N/A	46.5% n=919[121]	16.40%	28.53%	24.72%	13.66%	29.48%	23.75%

Uncovering Features for Predicting Hypotension

Machine learning is employed to uncover clinical and patient features that can predict hypotension. This allows for potential clinical practice guideline modification and/or early provider intervention to mitigate the effect. Our study consists of three folds. First, we use 561 observations from the first nine months (January – September 2014) and partition them randomly into two sets for training and blind prediction (as shown in Table 3-11). Next, we use the established predictive rules to blind predict the future three months of 189 patients (October to December 2014). And finally we blind predict 1,398 patients from the period January to September 2015. This allows us to measure the accuracy in predicting status of future patients. It also sheds light on the consistency of the physicians' hypotension definition.

Table 3- 11. Distribution of patient cases randomly selected for training and for blind prediction

	*Hypotension	No Hypotension	Total
Training set (observed cases from January – September 2014)	206	218	424
Blind Prediction (observed cases from Jan – Sep 2014)	72	65	137
Blind Prediction (observed cases from Oct – Dec 2014)	105	84	189

Table 3- 11. Continued

Total (observed cases for 2014)	383	367	750
Blind Prediction (chart review data from Jan – Aug 2015)	782	616	1398

*Documented by physicians as hypotension based on their own criteria.

Inputs to the computations consist of patient demographics, physical and allergy characteristics and overall health, weeks of pregnancy, number of redo epidurals, number of reboluses and dose, test dose, epidural needle/catheter dose, total dose, duration of injection, sensory level and time achieved, delivery type, position, medication type, and provider. Using the DAMIP machine learning algorithm, we seek to uncover a small subset of discriminatory features that can predict hypotension. DAMIP returns 27 predictive rules that result in greater than 82% 10-fold cross-validation and greater than 85% blind prediction for predicting hypotension and non-hypotension in patients for the period January – September 2014. The discriminatory features selected include weeks of pregnancy, number of redos, epidural needle/catheter dose, number of reboluses and dosage, and patients' allergy. When blind predict against new patients from October – December 2014, the predictive accuracy reaches 89%. Further, it reaches > 85% when blind predicting patients from January – August 2015. Table 3-12 contrasts the performance of DAMIP against other well-known classifiers. Compared to other classifiers, we note the consistently good predictive accuracy of DAMIP in both hypotension and non-hypotension patients.

Identified provider practice features offer an opportunity for CPG improvement, whereas patient characteristics allow for special care intervention during epidural process. In the simulation study below, we use the identified predictive rules and their associated

discriminatory features to construct care / delivery redesign experiments in an attempt to reduce hypotension incidence.

Table 3- 12. DAMIP classification results for predicting hypotension and comparison against other classifiers

Classifier	10-fold cross validation (424 cases) unbiased prediction estimate			Blind Prediction on 137 cases (January – September 2014)			Blind Prediction on 189 cases (October – December 2014)		
	<i>Overall Accuracy</i>	<i>Hypotensi on</i>	<i>Normal</i>	<i>Overall Accuracy</i>	<i>Hypotensi on</i>	<i>Normal</i>	<i>Overall Accuracy</i>	<i>Hypotensi on</i>	<i>Normal</i>
Classification Tree	65.60%	71.61%	51.76%	51.09%	73.85%	30.56%	59.79%	79.05%	35.71%
Logistic Regression	74.69%	88.24%	43.53%	47.45%	61.54%	34.72%	57.67%	67.62%	45.24%
Naive Bayes	73.80%	87.47%	42.35%	43.07%	78.46%	11.11%	58.20%	89.52%	19.05%
Random forest	76.83%	98.21%	27.65%	46.72%	96.92%	2.78%	56.08%	100.00 %	1.19%
k-nearest neighbors	66.31%	86.19%	20.59%	38.69%	80.00%	15.28%	56.08%	86.67%	17.86%
Support vector machine	60.61%	68.29%	42.94%	49.64%	69.23%	31.94%	52.38%	72.38%	27.38%
DAMIP	82.30%	82.50%	82.00%	89.00%	90.70%	87.50%	90.40%	89.20%	91.40%

System Simulation and Clinical Practice Improvement

We first ran the computer simulation model using parameters from the 750 observed cases. The simulation was run on 19,651 patients to approximate the total number of babies delivered during a calendar year. We focused on highly revealing issues based on outcome findings: re-do epidural procedure, hypotension and other complications such as blood in catheter/needle, wet tap, high block, and nausea and vomiting. Expected time for

completing the entire epidural workflow was 9.26 minute under current conditions. The first column in Table 3-14 shows the simulation results for one year. The resulting complication rates were compared to those of the 1,398 validated cases. Each complication is within 2-3% of its actual occurrence rate, indicating that the simulation reflects closely the hospital data.

Guided by the results from machine learning and the identified discriminatory features, we optimize the needle-base epidural dose administration process and report briefly the anticipated changes from current practice on three scenarios. These scenarios focus on physicians' variations on administering medication, test dosage and total dosage. Each scenario is characterized by the physician's individual epidural technique. In our simulation model, each scenario reflects actual physicians' characteristics such as selecting medications, loss of resistance technique and injecting durations.

Table 3- 13. Simulation scenarios performed to investigate potential reduction in complications

	Needle dosage: 15-18 ml (Scenario 1)	Needle dosage: 20-25 ml (Scenario 2)	Variable Dose Technique: (Scenario 3)
Test dosage	2 ~ 5 ml	0 ~ 5 ml	0 ~ 5 ml
Epidural needle dose	15 ~ 18 ml	20 ~ 25 ml	5 ~ 20 ml
Total dosage	15 ~ 25 ml	20 ~ 30 ml	10 ~ 30 ml

Scenario 1 reflects a moderate needle dose with a tight total dose across all practitioners (15-18 ml). Scenario 2 allows for higher needle dose up to 25 ml. Scenario 3 offers broader dose variance reflecting current practice while limiting needle dose to 20 ml. Table 3-14 shows that Scenario 1 results in the lowest re-do rate, hypotension rate and total procedure time than the other two scenarios; whereas Scenario 3 shows acceptable results

on hypotension. Overall, all three scenarios improve the procedure time. Using high epidural needle dose, Scenario 2 performs worse than the current practice. For the 1,398 chart review cases, the hypotension rate is 21% among patients satisfying Scenario 1 criteria.

Table 3- 14. Contrast of complication rates using 3 scenarios of needle-based approach

Complication	Occurrence rate per year: Current performance		Scenario 1	Scenario 2	Scenario 3
<i>Re-do epidural process</i>	Needle	5.14%	4.18%	4.75%	4.92%
	Catheter	5.15%			
<i>Replace epidural</i>	2.80%		2.40%	2.88%	3.02%
<i>*Hypotension</i>	50.89%		31.82%	55.43%	49.47%
<i>Blood in catheter/needle</i>	0.32%		0.31%	0.32%	0.33%
<i>Wet tap</i>	0.17%		0.16%	0.18%	0.17%
<i>High block</i>	0.33%		0.33%	0.33%	0.33%
<i>Nausea/Vomit</i>	0.35%		0.34%	0.35%	0.35%
<i>Faint</i>	0.17%		0.17%	0.16%	0.17%
Procedure time	9.26 minutes		5.12 minutes	5.98 minutes	5.78 minutes

*Based on definition of hospital providers.

Practice Variance among Providers

Forty-four physicians were observed. The years of practice ranges from 6 to 30 years. All physicians report using needle-based approach with over 68% acquired this skill at this hospital.

The top five medications are used in over 50% of the patient cases. The most commonly used medication (Table 3-7) is chosen by every physician. Categorizing physicians by years of practice: greater than 25 years (long), between 10 to 25 years

(medium), and fewer than 10 years (short), reveals that physicians are consistent in the delivery dosage. There is no significant difference in their epidural dosage for C-section (long vs medium: $p < 0.8590$, short vs medium: $p < 0.6623$, long vs short: $p < 0.8245$).

About 43.52% of providers favor the use of air in the loss of resistance technique (Figure 3-12, left). When comparing the time to sensory level versus different loss of resistance techniques, a significant difference is observed while the height, weight, and age of patients are similar across the preference techniques. When the loss of resistance utilizes air with local anesthetics, the average time to sensory level and frequency of re-bolus are lowest among all other techniques (Figure 3-12, right and Table 3-15).

While there is marginal difference in epidural replaced rate, overall redo rate appears to be lowest among physicians with medium years of experience. This may be explained that they have adequate experience and knowledge and are in good physical condition to deliver high quality service. The statistics also show that experienced physicians have the lowest redo rate in loss of resistance (Figure 3-13).

An online survey was used to capture physicians' self-reported definition for hypotension. Table 3-16 reports the number of hypotension cases and physicians' adherence to their own definition. "20% off baseline systolic" is the most common definition used by the providers; with 23 of them not only follow quantitative standard, but also pay attention to the patient's symptom.

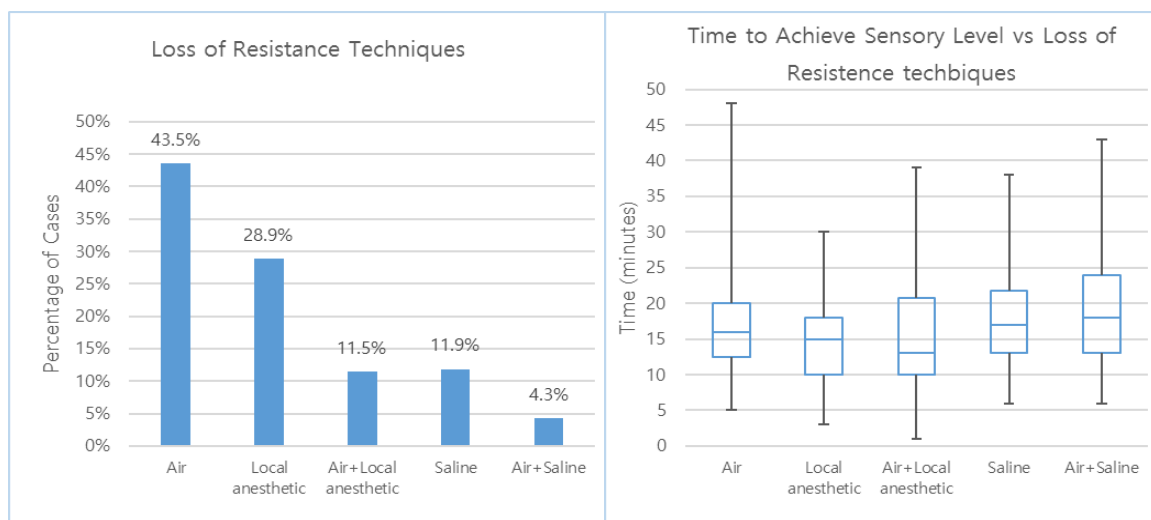


Figure 3- 12. Loss of resistance techniques versus the time to achieve desired sensory level

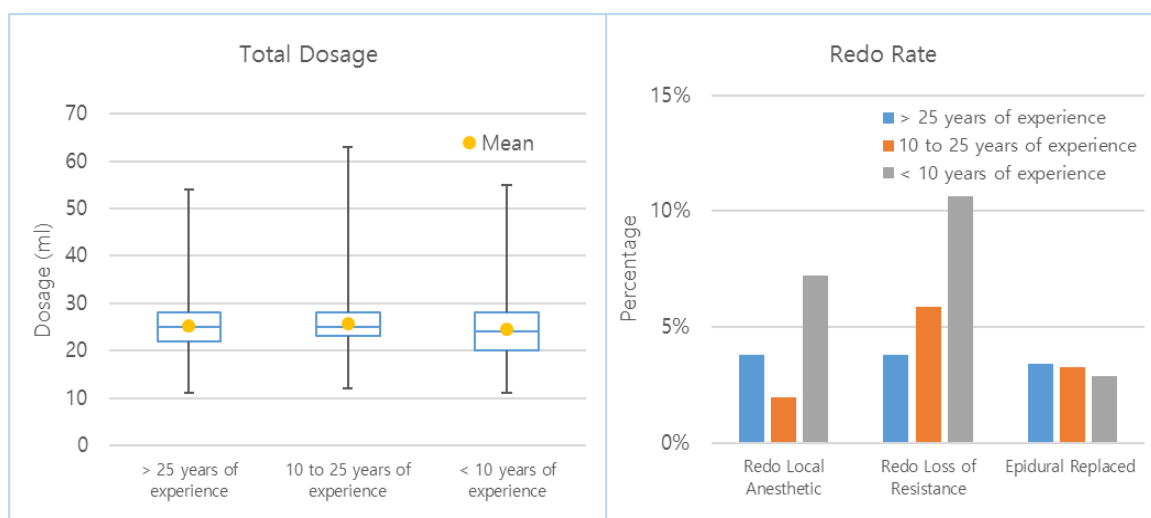


Figure 3- 13. Total dose versus redo rate break down by years of experience for needle-based approach

Table 3- 15. Frequency of re-bolus with different loss of resistance techniques

Loss of Resistance Technique	Air	Local anesthetic	Air + Local anesthetic	Saline	Air + Saline
Frequency of Re-bolus	27.66%	32.05%	17.74%	25.00%	37.50%

Table 3- 16. Self-report definition for hypotension and their observed compliance rates

Hypotension definition	No. of providers	Average compliance rate with self-definition
<i>20% off baseline, systolic</i>	15	110/168
<i>Below 90mmHg, systolic</i>	8	24/72
<i>Below 90mmHg, systolic or 20% off base line, systolic</i>	4	27/44
<i>Below 100mmHg, systolic or 20% off baseline, systolic</i>	2	22/27
<i>Below 80mmHg, systolic or 20% off baseline, systolic</i>	1	3/3
<i>15% off baseline, MAP<55</i>	1	4/9
<i>20% off baseline, MAP<55</i>	1	13/17
<i>30% off baseline, systolic</i>	1	3/10
<i>Total reported</i>	33	206/350
<i>Not reported</i>	11	N/A/33
Total	44	383

3.2.4 Discussion

Of the 3,988,076 documented births in the United States in 2014, 32.2% were delivered via cesarean delivery; and among women delivering vaginally, as high as 61% received a neuraxial block. The potential consequences of a failed or misplaced epidural needle are well known to anesthesiologists who practice obstetric anesthesia. While much has been analyzed regarding complications, especially hypotension, there has been limited research regarding the dose-sensory response and standardization of the epidural analgesia procedure to reduce practice variance and maintain low rates of complication. Moreover, little is known regarding practice and patient outcome related to large dose injected through the epidural needle.

With increasing demand on quality of medical service and evidence of outcome, the medical providers seek to work collaboratively with systems engineers to comprehensively analyze the performance of the epidural anesthesia service. Specifically, we analyze and quantify the dose-sensory response evidence and the associated complications in the hands of experienced anesthesiologists. We also evaluate the safety of a needle-based epidural technique for elective caesarian sections and establish evidence of a safe-level of epidural needle dose. To the best of our knowledge, there is no previous comparative effectiveness study analyzing dosage delivered via needle versus catheter.

The analysis involves two cohorts of pregnant women who received epidural analgesia procedure: 750 in 2014 and 1,398 in 2015. First, the team shadowed the anesthesiologists and observed in-depth the epidural procedure for the 750 patients. The duration and dose required to achieve the desired sensory level and associated complications were captured.

To establish the foundation for comparison, we first analyze the physical and medical background of these patients for the needle-based and catheter-based approaches. Our findings indicate that there is no significant difference among these patients in terms of weight, height, and weeks of pregnancy. But we did find that C-section patients are older than those women who choose natural birth. This is consistent with the national statistics.

Among these 750 patients, the results show that needle-based approach is faster (15.63 minutes versus 20.00 minutes) and more dose-effective (requiring less dose, mean 24.99 ml versus 30.27 ml) in achieving comparable sensory level than the traditional catheter-based approach. Our findings also reveal that injecting large doses (up to 20 ml) in the epidural space through the epidural needle is safe and results in good outcome for the patients. The associated complications (hypotension, epidural replaced, wet tap, blood

in the catheter/needle, high block, and nausea and vomiting) are similar to those reported in published literature. Further, if the needle dose is kept under 18 ml, the resulting hypotension rate will be significantly lower (60% reduction from 52.32% to 21%, using the hospital's definition).

Time to sensory level is an important measurement of quality of care. With shorter time and less dosage of medication to sensory level, mother and fetus also face less risk regarding complications, such as hypotension, nausea and fetal bradycardia.

Using a DAMIP machine learning approach, we rank the significance of clinical, patient, and epidural procedural factors in affecting hypotension. In particular, we identify a small subset of discriminatory features, including weeks of pregnancy, patient allergies, number of redos, epidural needle/catheter dose, and number of reboluses and dosage that can predict hypotension with 85% confidence.

The identified patient characteristics (weeks of pregnancy, allergies) allow for precautionary care intervention for at-risk patients during the epidural procedure. The provider practice features (epidural needle/catheter dose, number of redos, reboluses and dosage) offer an opportunity for clinical practice guideline development and process improvement. Using system simulation and optimization, we investigate scenarios to reduce the hypotension incidence. In particular, we focus on a CPG with three factors: test dose, needle dose, and the total dose of the epidural. Under this CPG, the hypotension rates can be driven down to 31% while the needle dose can be as high as 18 ml.

A second cohort of 1,398 patients obtained via chart review is used to validate our findings to ensure that they are representative of the hospital clinical practice. We note that similar results are concluded in these patient cases, and that the DAMIP classification rule

can predict the hypotension of these patients with 85% accuracy. Further, under the needle-dose of 18 ml, the hypotension complication rate is approximately 21%.

We contrast the proficiency of physician practice and provide insights on their preference in medication and dosage. Understanding the causes and effects of variation can help providers and healthcare organizations avoid practices that negatively impact outcomes. Our results establish evidence of safe and effective epidural needle dosage. This facilitates evidence-based dose delivery to patients that results in safer and more effective pain control during child delivery. The new CPG results in fewer complications and helps with training of anesthesiologists based on evidence-based best practice.

Injecting large doses through the epidural needle is not without risk. Only experienced anesthesiologists should attempt this technique. Even experienced anesthesiologists should be prepared to immediately treat total spinals with airway and hemodynamic control and Intralipid should be available for inadvertent venous injections.

Acknowledgment

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CHAPTER IV

COMPUTATIONAL IN-SILICO DRUG DESIGN

The drug discovery and drug development is long, costly and complex process[8]. Implementing new strategy in drug development requires practical process innovation to accelerate drug development. Here, theoretical and practical approach involves three major pieces 1) identifying critical processes in each phase on drug development, 2) building critical process model to accelerate drug development, and 3) suggesting possible scenarios to reduce cycle time from beginning to marketing in drug development.

In this chapter, we describe the first in-silico drug design system model to accelerate drug discovery. Our model spans preclinical research, the IND review, clinical research, and the NDA review. We identify the global process for any drug discovery pathway with timeline along the entire system process. Next, we identify bottlenecks, and perform system optimization that offers a holistic view of discovery pathways. The integration of bottlenecks into possible candidate tasks which can be conducted simultaneously highlights critical paths for the accelerated development process. We define the critical paths as parallel model for the new drug development. Our generalized parallel model allows not only rapid development but also processes that minimize risk, cost, and time.

4.1 Transforming Drug Development Via System Computational Modeling

4.1.1 Introduction

The drug discovery and drug development is long, costly and complex process[8]. The cost of drug development has risen markedly in the past 30 years [122-124]. The fully loaded cost to discover and develop a new drug is the highest it has ever been and is increasing exponentially[123]. Even the number of drugs approval rate have been marked as the lowest recently[125]. The time to discover and develop drugs is also significantly increasing. As a result, the pharmaceutical industry has been facing tremendous pressure, not only increasing R&D expenditure but also consequently rising health care cost in the society. Therefore, drug companies are under pressure to demonstrate that their products offer therapeutic or cost advantage over competitors' products and non-pharmaceutical treatment options[124].

On the public sector's standpoint, drug discovery and drug development has risen as important issue on several ways. First of all, serious outbreak of disease requires accelerated drug discovery and drug development. During nine months till the middle of December in 2014, more than 19,000 people were infected by Ebola virus and lots of the patients around 40% were dead by the Ebola virus disease(EVD). The outbreak through the year seems to keep increasing the number of cases and deaths unless efficient drugs or vaccines would not be provided. Since the first case of EVD was reported in March 2014, the outbreak has continued and the total number of 19,065 patients was reported as the confirmed or suspected in the EVD-affected countries, mostly happen in the three outbreak countries(Guinea, Liberia, and Sierra Leone)[126]. However, available therapeutics to treat the infected patients or vaccines to prevent people from infection is currently not developed

yet. Thus, saving stockpile of vaccines after quick process of development is considered as the most effective way to prepare the crises related to the biological agents such as EVD. Another issue on the drug discovery and drug development in the public sector is responding bioterrorism. After 9/11 terrorist attacks, additional attacks happened on 5 October in 2001 using anthrax. The anthrax attacks revealed gaps in knowledge that compromise the ability to respond to a bioterrorist attack[127]. When the attacks happened, the appropriate antibiotic drugs to use and the duration of treatment remained uncertain. Therefore, immediate responses to the potential threats of bioterrorism attacks needs to be addressed.

Several efforts to fulfill the needs of accelerated new drug discovery and drug development have been issued for a long time. Firstly, the Food and Drug Administration(FDA) has tried to expedite development and approval process with various attempts. The first program was “orphan drugs”, which helps a limited category of drugs to be provided to the market more efficiently in 1983[128]. After the first program, “fast track” was introduced in 1988 as a second program to expedite the development and evaluation process of new drugs for serious or life-threatening diseases[128]. In 1992, the “accelerated approval” pathway was created to accelerate approval of particular investigational drugs, allowing approval based on surrogate endpoints in place of clinical endpoints. Also, “priority review” program was initiated in 1992, to expedite FDA review of a completed new drug application(NDA)[128]. In 2012, Congress created the “breakthrough therapy” designation, which may be based on surrogate endpoints, receive greater FDA resources to expedite their development and approval. However, these expedited drug development and FDA programs lead some possible disadvantages such as drug safety concerns, insufficient or delayed studies to confirm preliminary evidence, potential industry capture associated with the fees paid for expedited review, and public misperception of the therapeutic value of drugs approved via expedited pathways.

Secondly, in 2004, the FDA has developed the Critical Path Initiative(CPI), a project that is intended to improve the drug and medical device development processes, the quality of evidence generated during development, and the outcomes of clinical use of these products[129]. The FDA identified the “Critical Path” as a process beginning with identification of a drug candidate and completing in marketing approval. Along the path to the final marketing approval phase, the new drugs are subjected to a series of evaluations to predict its safety and effectiveness. The FDA sets three dimensions along the critical path, safety, medical utility and industrialization. Through the CPI, FDA applies scientific tools to improve drug development process and reduce uncertainty in each dimension. The candidate must successfully complete a series of evaluations of its potential safety and efficacy at each step of three dimensions along the critical path and must be amenable to mass production. Although CPI provides critical steps and sophisticated scientific tools along the path to the final approval phase, deconstructing and innovating the drug development process is still required[128-130].

Thirdly, some previous research has been attempting to improve R&D productivity in drug development. Paul et al. defines R&D productivity as two important dimensions: R&D efficiency and R&D effectiveness[124]. They build a model of R&D productivity to understand the interdependencies between inputs, output and outcomes. They also suggest work in process, value, cycle time, cost, and probability of technical success as key areas for improving R&D productivity. Conclusively, they contrast new drug development paradigm to traditional pipeline along with concepts such as critical chain of project tasks, adaptive and seamless process design, and portfolio selection in which lead dynamic transaction of information and fast feedback on pathway to launch new drugs. Meanwhile, DiMashi suggests quick development and earlier termination decisions to reduce R&D cost and failure rate, so that company can reinvest savings to another agent[131]. He focuses on

improving attrition in early development phase and inducing decision making point shifted to earlier phase to save capitalized clinical cost.

Another approach to innovate drug development and drug discovery is model-based approach. Lalonde et al. and Zhang et al. apply model-based drug development to focus on mathematical models to characterize the input-output relationship within disease and drug models for knowledge management and decision making[130, 132]. They suggest methodology to apply model-based drug development as three steps: knowledge gathering, model construction and simulation of outcome. This approach is similar to FDA's CPI approach because it applies quantitative tools in each step and simulates model to clear uncertainty along the entire development process.

Many previous researches have shown the clues for accelerating drug development and drug discovery. However, implementing new strategy in drug development requires practical process innovation to accelerate drug development. With the emphasis on acceleration, possible number of options can be considered. Lesko et al. suggests five options[133]: 1) paralleling or overlapping phases of clinical development, 2) intensifying efforts in a given phase of drug development, 3) combining multiple objectives and efforts, 4) simplifying clinical programs and shortening timelines, 5) skipping or postponing studies. Taking FDA's CPI into account, accelerating drug development should be placed on the deconstructing current process on first hand. Then, paralleling and combine each phase to facilitate accelerated drug development process is required.

With this framework in mind, this paper aims to study drug development and drug discovery process, particularly identifying critical process to achieve the goal of each phase. Each big phase on the drug development pathway has its own agenda to achieve. Some

process steps strongly affect the goal but others are not. Specifically, we focus on three areas:

1. *Identify critical processes in each phase on drug development and drug discovery.* Since drug development pathway consists of lots of steps to evaluate new drug's safety and efficacy, we first focus on identify overall processes along the whole pathway. Then, we figure out critical processes in each phase to build parallel process model.
2. *Build critical process model to accelerate drug development and drug discovery.* After identifying critical processes in each phase, we manage to connect each critical processes taking paralleling and intensifying processes into account. As a result, general drug development model and critical path drug development model can be presented and compared. Then, we focus on the variations between the two development models.
3. *Suggest possible scenarios to reduce cycle time from beginning to marketing in drug development and drug discovery.* Based on both general drug development and critical path drug development models, we aim to show possible scenarios to reduce total cycle time to complete drug development processes using computerized simulation model.

4.1.2 Drug Development Process Model

New drug development can proceed along varied pathways for different compounds, but a development paradigm has been articulated that has long served well as a general

model[134]. In outline form, the paradigm portrays new drug development as proceeding in a sequence of phases. The process and time course from drug discovery to approval for marketing is shown in Figure 4-1.

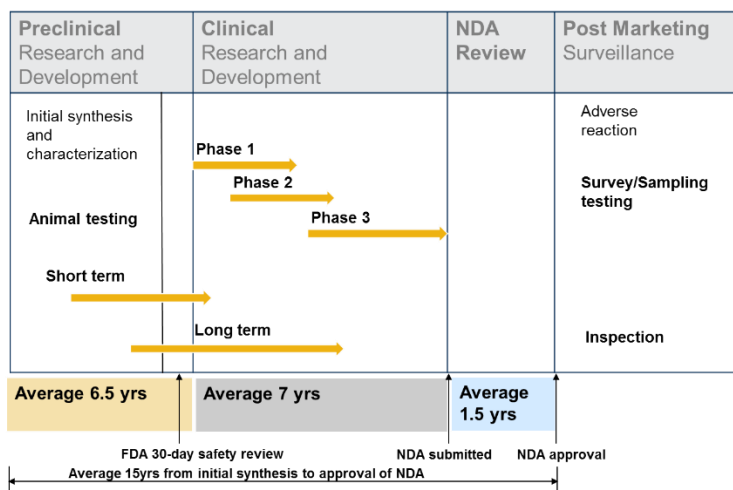


Figure 4- 1. The New Drug Development Process[135]

This paper studies sequence of phases in new drug development as: (1) preclinical research, (2) IND review, (3) clinical research and (4) NDA review. All processes would be applied to develop new drug under general principle even though they could be skipped and modified according to types of drug.



Figure 4- 2. Phases of New Drug Development Process[136]

Preclinical Research

As part of the drug discovery process, using chemical library profiling and lead compound optimization, the many thousands of compounds synthesized and tested in high-throughput biological activity screens are narrowed down to relatively few compounds that will be evaluated in Phase 1. The purpose of the preclinical phase is to further narrow drug candidate selection for subsequent evaluation in humans. This is achieved through in discovery, formulation study, efficacy study, safety study, and animal testing. A broad, general goal is to integrate knowledge gained from this phase into the decision-making process in the design and conduct of early clinical studies. When it occurs and is bidirectional, this integrative process provides a better understanding of the mechanism of drug action, suggests improved animal models to evaluate drug targets and drug-disease interactions, and helps to design animal experiments that, as second-generation compounds are studied, provide more clinically useful information, predict drug class liability with respect to safety, and generate exposure-response relationships for efficacy and safety that can be extrapolated from animals to humans.

The first step of preclinical phase is target discovery, which focuses on understanding the disease targets. Target discovery is highly depending on a detailed knowledge of the disease and it involves target isolation and purification, in vitro and in vivo assay development and testing of compounds. During the target discovery process, new drug substances are identified through target identification, screenings, structure modification and formulation study. Once new drug substances are found, two types of preclinical research need to be done: pre-clinical efficacy evaluation and preclinical safety evaluation. Both processes are biochemical evaluations to ensure effectiveness and safety subject to animals. In preclinical efficacy evaluation, pharmacology study, pharmacokinetics(PK) study and pharmacodynamics(PD) study are main tasks. If the efficacy evaluation is not satisfied, then the new drug substances would be revisited on

formulation study and they would be modified to enhance efficacy. Likewise, over the pre-clinical safety evaluation, toxicity study, ADME(absorption, distribution, metabolism, excretion) test, and chronic toxicity study are performed.

As a promising new drug substances are characterized for biological activity, they are also evaluated with regard to chemical and physical properties that have bearing on its ultimate and successful formulation into stable and effective pharmaceutical products before formulating initial products. In this early formulation study, preformulation tests such as drug solubility, partition coefficient, dissolution rate, physical form and stability are evaluated to support producing initial products. In the meantime, the sponsor of new drug is preparing IND review and research agency is preparing for Phase 1 and Phase 2 for clinical trials.

Table 4- 1. Process of Preclinical Research

Process	Tasks
<i>Discovery</i>	High-Throughput Screening
	Structure/Molecular Modification
	Mechanism-Based Design
<i>Preclinical research: Efficacy</i>	In-Vitro Testing
	In-Vivo Testing
	ADME Testing
	Pharmacodynamics Study
<i>Preclinical research: Safety</i>	Acute Toxicity Study
	Subacute Toxicity Study
	Chronic Toxicity Study
	Reproduction/Mutagenicity Study
<i>Preclinical research: Early formulation study</i>	Drug Solubility Test
	Partition Coefficient Test
	Dissolution Rate Test
	Physical Form Test
	Stability Test

IND Review

Under the Food, Drug, and Cosmetic Act as amended, the sponsor of a new drug is required to file with the FDA an Investigational New Drug Application(IND) before the drug may be given to human subjects. This is to protect the rights and safety of the subjects and to ensure that the investigational plan is sound and is designed to achieve the stated objectives[135]. When the IND is received by the FDA, the IND is forwarded to appropriate division and the content of the application is thoroughly reviewed to determine whether the preclinical data indicates that the new drug is sufficiently safe for administration to human subjects and that the proposed clinical studies are designed to provide the desired data on drug safety and efficacy while not exposing the human subjects to unnecessary risks. The IND review has “30-day Response Clock” policy that FDA is required by the Modernization Act to respond in writing to an IND sponsor within 30 calendar days of receipt of the sponsor’s complete response to a clinical hold[81]. Figure 4-3 shows the IND review process.

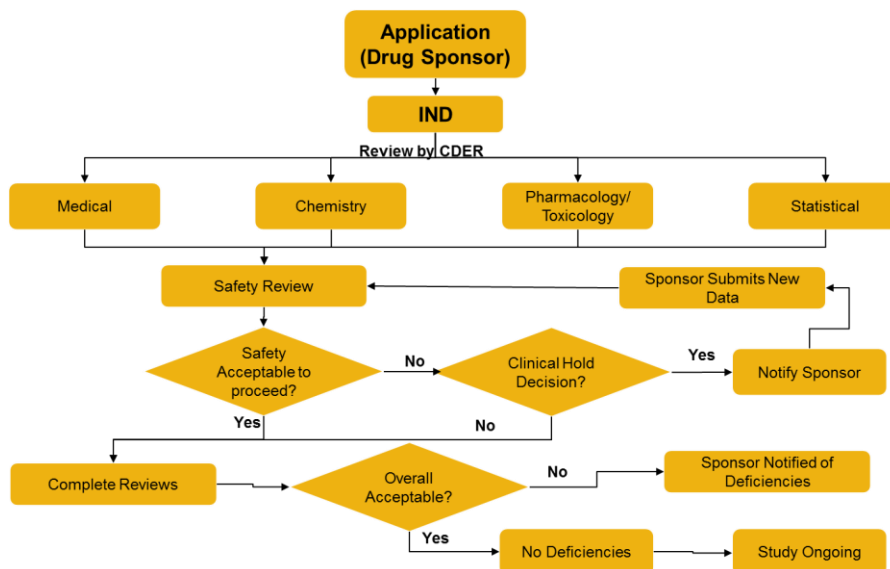


Figure 4- 3. IND Review Process

Clinical Research

Clinical research typically proceeds through three successive phase[134]. In Phase I, a small number of usually healthy volunteers are tested to establish safe dosages and to gather information on the absorption, distribution, metabolic effects, excretion, and toxicity of the compound. Phase I is sometimes split into two steps with regard to amount of dosages. The first step of Phase I is single ascending dose(SAD) study, which is small groups of subjects are given a single dose of the drug while they are observed and tested for a period of time to confirm safety[137]. Typically, a small number of participants, usually three, are entered sequentially at a particular dose. If they do not exhibit any adverse side effects, and the pharmacokinetic data are roughly in line with predicted safe values, the dose is escalated, and a new group of subjects is then given a higher dose. If unacceptable toxicity is observed in any of the three participants, an additional number of participants, usually three, are treated at the same dose. This is continued until pre-calculated pharmacokinetic safety levels are reached, or intolerable side effects start showing up at which point the drug is said to have reached the maximum tolerated dose[138]. The second step of Phase I is multiple ascending dose(MAD) study that studies investigate the pharmacokinetics and pharmacodynamics of multiple doses of the drug, looking at safety and tolerability. In these studies, a group of patients receives multiple low doses of the drug, while samples are collected at various time points and analyzed to acquire information on how the drug is processed within the body. The dose is subsequently escalated for further groups, up to a predetermined level[137]. While MAD study is on progress, food effect test could be designed to investigate any differences in absorption of the drug by the body, caused by eating before the drug is given. If Phase I studies demonstrate sufficient merit and if the order of drug toxicity is low enough, Phase II begins, studying up to several hundred patients.

Phase II is conducted with subjects who have the targeted disease or condition and are designed to obtain evidence on safety and preliminary data on efficacy[134]. Phase II is also divided into two steps like Phase I studies. The former part of Phase II is pilot study which is specifically designed to assess dosing requirements and the latter part of Phase II is pivotal study which is specifically designed to study efficacy. During Phase II studies, the new drug product is refined, with the final formulation developed for use during Phase III studies.

The final Phase III typically consists of a number of large-scale trials that are designed to assess the effectiveness of the new intervention and, thereby, its value in clinical practice. Many additional clinicians having patients with the condition for drug's intended use are recruited to participate in this study. Several dosage strengths of the proposed new drugs may be evaluated during this Phase III, using formulations intended to be proposed in the new drug application(NDA) and for marketing[135]. Sufficient information on the new drug's effectiveness and safety is expected to be collected during Phase III.

Table 4- 2. Process of Clinical Research

Process	Tasks
<i>Clinical Research: Phase I</i>	SAD Test
	MAD Test
	Food Effect Test
<i>Clinical Research: Phase II</i>	Pilot Study in Phase II
	Pivotal Study: Efficacy Test
<i>Clinical Research: Phase III</i>	Pivotal Study in Phase III
	Additional Study for Regime
	Long-term Study

The New Drug Application

If the three clinical phases during the IND period demonstrate sufficient drug safety and therapeutic effectiveness, the sponsor may file a NDA with the FDA. The completed NDA is carefully reviewed by the FDA, which decides whether to allow the sponsor to market the drug, to disallow marketing, or to require additional data before rendering a judgement[135]. By regulation, the FDA must respond within 180 days of receipt of an application[137]. However, it generally takes more than 6 months for sponsor to fulfill the requirement of the NDA, sometimes takes up to 7 years to get the approval to market the drug[125, 137]. Figure 4. shows the NDA review process.

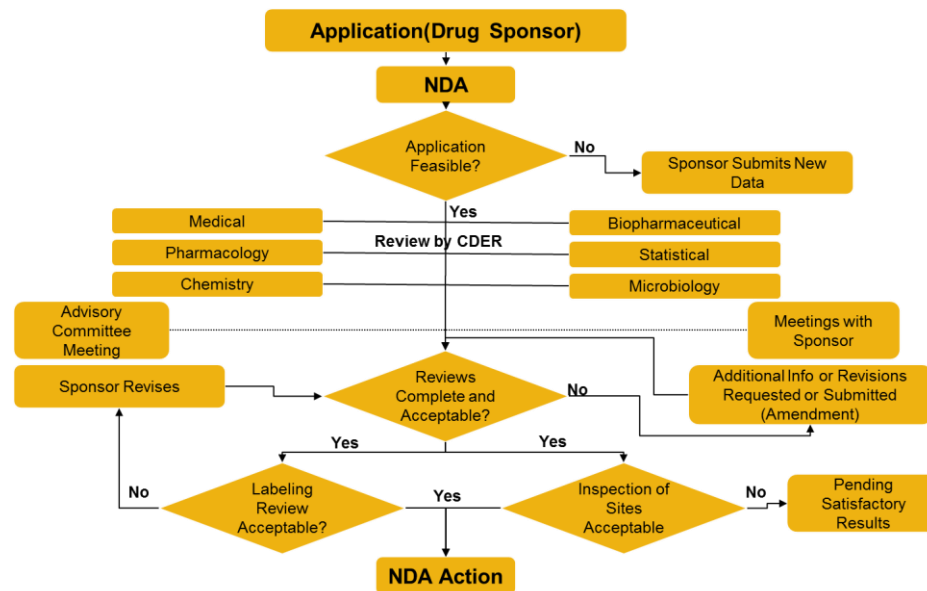


Figure 4- 4. The NDA Review Process

4.1.3 Critical Path Model and Simulation Study

Simulation Results from Current Sequences of the New Drug Development Process

In this part, we first attempt to run current new drug development process suggested in section 2. Taking into account of deconstructing of new drug development[130, 139, 140],

optimizing drug development strategy[81, 132, 141], and productivity[124, 125, 129, 131], we aim to two simulation models: from beginning to the IND review and from beginning to the completion of the NDA review. The former simulation model could help the pharmaceutical companies to make early termination of the new drug development and the latter model could spotlight overall R&D time consuming if they maintain to adopt the series of current new drug development process.

Statistics and anticipated times consuming on the tasks of new drug development process are gathered from various sources[135, 137, 138, 142] and experts from pharmaceutical industry. Collecting process time, we decide some of the process times as fixed number if they maintain very minimum variations while we set triangular, normal or uniform distributions to the process times if they are highly volatile. All distribution sets are determined with reasonable considerations among researchers. Table 4-3 shows simulation input table and Table 4-4 shows success rate of each test.

Table 4- 3. Simulation Input Table

Process	Tasks	Time	Distribution(days)
Discovery	<i>High-Throughput Screening</i>	Avg. 4~6 weeks	Triangular(28, 42, 38)
	<i>Structure/Molecular Modification</i>	Avg. 3 ~ 5 weeks	Triangular(20, 27, 33)
	<i>Mechanism-Based Design</i>	Avg. 2 weeks	Triangular(12, 18, 15) Normal(14, 4)
Pre-clinical research: Efficacy	<i>In-Vitro Testing</i>	14 days	Fixed Delay
	<i>In-Vivo Testing</i>	28 days	Fixed Delay
	<i>ADME Testing</i>	5 -10 days	Fixed Delay: 7 days
	<i>Pharmacodynamics Study</i>	Avg. 2 weeks	Normal (14, 2)
Pre-clinical research: Safety	<i>Acute Toxicity Study</i>	Avg. 1 day	Triangular(0.5, 1.2, 1) Normal(1, 0.9) Uniform(0.5, 1.2)
	<i>Subacute Toxicity Study</i>	Avg. 2 weeks	Triangular(12, 16, 14) Normal(14, 2) Uniform(12, 16)
	<i>Chronic Toxicity Study</i>	90 ~ 180 days	Triangular(90, 180, 160)

Table 4- 3. Continued

	<i>Reproduction/Mutagenicity Study</i>	Up to 18 ~ 24 months	Triangular(500, 740, 660)
Pre-clinical research: Early formulation study	<i>Drug Solubility Test</i>	Avg. 1 month	Fixed Delay: 30 days
	<i>Partition Coefficient Test</i>	Avg. 1 month	Fixed Delay: 30 days
	<i>Dissolution Rate Test</i>	Avg. 1 month	Fixed Delay: 30 days
	<i>Physical Form Test</i>	Avg. 1 month	Fixed Delay: 30 days
	<i>Stability Test</i>	Avg. 1 month	Fixed Delay: 30 days
IND Review	<i>IND Review</i>	30 days	Fixed Delay
Clinical research: Phase 0	<i>Pre-Clinical Research Test</i>	30 ~ 60 days	Triangular(30, 60, 50)
Clinical research: Phase 1	<i>SAD Test</i>	180 ~ 240 days	Triangular(180, 240, 215)
	<i>MAD Test</i>	180 ~ 240 days	Triangular(180, 240, 212)
	<i>Food Effect Test</i>	Avg. 60 days	Uniform(50, 70)
Clinical research: Phase 2	<i>Pilot Study in Phase 2</i>	150 ~ 180 days	Triangular(90, 180, 160)
	<i>Pivotal Study: Efficacy Test</i>	180 ~ 720 days	Triangular(180, 720, 600)
Clinical research: Phase 3	<i>Pivotal Study</i>	360 ~ 1100 days	Triangular(360, 1100, 850)
	<i>Additional Study for Regime</i>	Avg. 1 month	Fixed Delay: 30 days
	<i>Long-term Study</i>	360 ~ 2160 days	Triangular(360, 2160, 1790)
NDA Review	<i>NDA Review</i>	Avg. 540 days	Uniform(500, 600) Triangular(480, 660, 550)

Table 4- 4. Success rate of each test

Decision Nodes	Success Rate
<i>Discovery Test</i>	10~25%
<i>Efficacy Test</i>	5~12%
<i>Safety Test</i>	3~9%

We generate 3 cases with respect to combinations of simulation input table: the shortest, the moderate, and the longest case. The success rate is randomly generated within given range in Table 4-4. Each case generates the expected processing time with at least 100 replications in simulation. The first simulation model which covers from beginning to the IND review completion results in 60 months for the shortest case, 64 months for the moderate case and 72 months for the longest case. The second simulation model which

covers from beginning to the NDA review completion provides outcome results as 180 months for the shortest case, 182 months for the moderate case and 199 months for the longest case. These timelines are similarly compatible with various research[123, 125, 129, 135] but longer than DiMasi et al[134]. Since DiMasi et al. found the average length of processing time from a survey of 10 pharmaceutical firms[134] while our simulation model suggests average length of processing time based on simulation generated with stochastic distribution, it might be different from each other with the nature of study scheme.

Table 4- 5. Simulation results from current new drug development process

Beginning to the IND review Completion	Case	Shortest	Moderate	Longest
	<i>Months</i>	60 months	64 months	72 months
	<i>Days</i>	1,807 days	1,915 days	2,161 days
	<i>Range</i>	1,756 ~ 1,900 days	1,800 ~ 1,975 days	2,092 ~ 2,400 days
Beginning to the NDA review Completion	Case	Shortest	Moderate	Longest
	<i>Months</i>	180 months (15 years)	182 months (15 years 2 months)	199 months (16 years 7 months)
	<i>Days</i>	5,411 days	5,441 days	5,972 days
	<i>Range</i>	5,263 ~ 5,568 days	5,355 ~ 5,530 days	5,708 ~ 6,915 days

Simulation Results from Parallel Model of the New Drug Development Process

After the demonstrating of the current new drug development process according to two simulation models, we find the critical path tasks to be centered in order to build parallel model. We adopt two principles to identify critical path and build parallel process. First of all, we figure out bottleneck tasks to delay total processing time. Since the bottleneck tasks make other tasks starving from global system viewpoint, we build parallel process

conducting some tasks simultaneously during performing bottleneck task. Secondly, we identify parallel model taking into account of not to break the exact sequences of the new drug development process. For example, even though certain tasks could be hooked up with bottleneck task, they might require prerequisite task to move on. In other words, we sort out each task as either possible candidate of parallel model or candidate to be conducted standalone. Table 4-6 presents summary of tasks in parallel model, which explains what tasks can be conducted simultaneously. Also, Figure 4-5 shows the critical path flow in the new drug development process. In Figure 4-5, the tasks marked with same color would be conducted simultaneously under parallel model.

Table 4- 6. Summary of tasks in parallel model

Parallel Group Tasks	Bottleneck
<i>High-Throughput Screening</i>	High-Throughput Screening
<i>Structure/Molecular Modification</i>	
<i>Mechanism-Based Design</i>	
<i>In-Vitro Testing</i>	ADME Testing
<i>In-Vivo Testing</i>	
<i>ADME Testing</i>	
<i>Acute Toxicity Study</i>	Reproduction/Mutagenicity Study
<i>Subacute Toxicity Study</i>	
<i>Reproduction/Mutagenicity Study</i>	
<i>Drug Solubility Test</i>	All Simultaneous Tasks
<i>Partition Coefficient Test</i>	
<i>Dissolution Rate Test</i>	
<i>Physical Form Test</i>	
<i>Stability Test</i>	
<i>IND Review</i>	Pre-Clinical Research Test
<i>Pre-Clinical Research Test</i>	
<i>MAD Test</i>	MAD Test

Table 4- 6. Continued

<i>Food Effect Test</i>	
<i>Pilot Study in Phase 2</i>	Pivotal Study: Efficacy Test
<i>Pivotal Study: Efficacy Test</i>	
<i>Pivotal Study</i>	Long-term Study
<i>Additional Study for Regime</i>	
<i>Long-term Study</i>	
<i>NDA Review</i>	Avg. 540 days

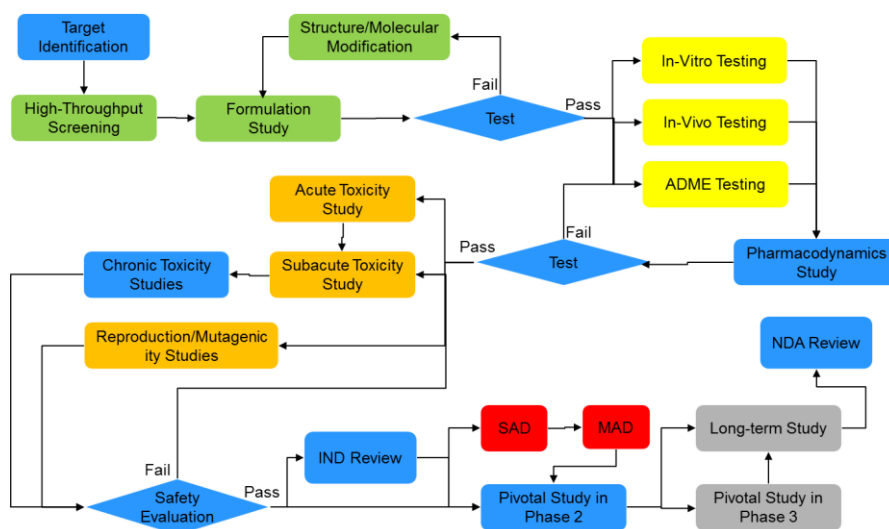


Figure 4- 5. Critical path flow in the new drug development process

Then, we run the two simulation models again based on parallel model with critical path to highlight the cycle time reduction. We apply same simulation input for the 3 cases and the success rate is randomly generated. Likewise, each case produces the expected processing time with at least 100 replications in simulation. Particularly, we examine the possibility whether the parallel model could achieve 36 months' range to complete up to the IND review task because we want to ensure that our model would be meaningful system to apply "quick win, fail fast" paradigm[124]. The first simulation model which covers from beginning to the IND review completion shows 30 months for the shortest case, 36

months for the moderate case, and 39 months for the longest case, that all results are generally satisfied with 36 months' cut considering nature of stochastic distribution. The second simulation model which covers from beginning to the NDA review completions results in 116 months for the shortest case, 130 months for the moderate case and 160 months for the longest case, that 20% ~ 36% of total cycle time reductions are expected with parallel model.

Table 4- 7. Simulation results from parallel model of the new drug development process

Beginning to the IND review Completion	Case	Shortest	Moderate	Longest
	<i>Months</i>	30 months	36 months	39 months
	<i>Days</i>	908 days	1,081 days	1,168 days
	<i>Range</i>	808 ~ 1,000 days	889 ~ 1,201 days	989 ~ 1,302 days
Beginning to the NDA review Completion	Case	Shortest	Moderate	Longest
	<i>Months</i>	116 months (9 years 8 months)	130 months (10 years 10 months)	160 months (13 years 4 months)
	<i>Days</i>	3,468 days	3,912 days	4,792 days
	<i>Range</i>	3,292 ~ 3,598 days	3,822 ~ 4,001 days	4,737 ~ 4,878 days



Figure 4- 6. Comparisons of the simulation results

4.1.4 Conclusion

We have described the first in-silico drug design system model to accelerate drug discovery. Our model spans preclinical research, the IND review, clinical research, and the NDA review. We first have identified the global process to be applied for any drug discovery path and then assigned time frame over the span. The estimated cycle time from computer simulations until completing the IND review would be more than 5 years and until getting approval of the NDA review would be more than 15 years, possibly more than 16 years if the new drug development process follows serial sequences. These simulation results prove why numerous attempts to accelerate the new drug development process have been done for the past two decades. In particular, the fact that faster development of the new drug reduces capitalized costs[131] has been shown empirically and improvements in the timing of early research termination on new drug are required under the circumstance that industry

clinical success rates have remained stable for a long time[8], it is clear that contributing solutions to achieve rapid drug development should be addressed.

Since identification and optimization of the critical path of the development tasks[124], telescoping and overlapping of development process[133], model-based drug development[130, 132, 140], and deconstructing the drug development process[129, 139] have been suggested as potential solutions, we try to identify bottlenecks, and perform system optimization that offers a holistic view of discovery pathways. The integration of bottlenecks into possible candidate tasks which can be conducted simultaneously highlights critical paths for the accelerated development process. We define the critical paths as parallel model for the new drug development. To verify effectiveness of our parallel model, we simulate two models, one for decision making of early termination and the other for the overall paths from start to registration of a new drug. Computer simulations show that parallel models up to the IND review reduce at least 40% processing time compare to serial sequence models, even up to 60% reduction could be possible. Also, simulations demonstrate that parallel models up to the NDA review reduce 20% to 36% ranges of total processing time compare to serial sequence models. Since empirical data suggests that 30% of phase-time reduction could induce about 20% of cost reduction, we believe that our parallel model would allow not only rapid development but also minimizing risk, cost, and time.

For the further study, we would like integrate our parallel model into R&D productivity and total cost measurement framework. This research focuses on processing time up to certain points on the new drug development pathways and measures risks and cost savings indirectly from empirical research. However, our computational model can generate productivity measures such as utilization rate and anticipate cost along with the development pathways. Therefore, we firmly believe that our model would be flexibly

adjustable for any input as well as methodologically useful for decision making under multiple criteria.

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